(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 399 414 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **21.09.94**

(51) Int. Cl.[5]: **C07D 211/46**, C07D 211/54, A61K 31/445

(21) Application number: **90109534.9**

(22) Date of filing: **19.05.90**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Piperidine derivative, method for preparation thereof, and a pharmaceutical composition comprising the same.**

(30) Priority: **22.05.89 JP 126596/89**
20.02.90 JP 37397/90

(43) Date of publication of application:
28.11.90 Bulletin 90/48

(45) Publication of the grant of the patent:
21.09.94 Bulletin 94/38

(84) Designated Contracting States:
CH DE ES FR GB IT LI SE

(56) References cited:
EP-A- 0 134 124
EP-A- 0 226 516
EP-A- 0 335 586

PATENT ABSTRACTS OF JAPAN vol. 11, no. 106 (C-414)(2553) 03 April 1987, & JP-A-61 254559 (TERUMO CORPORATION) 12 November 1986.

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Description

BACKGROUND OF THE INVENTION

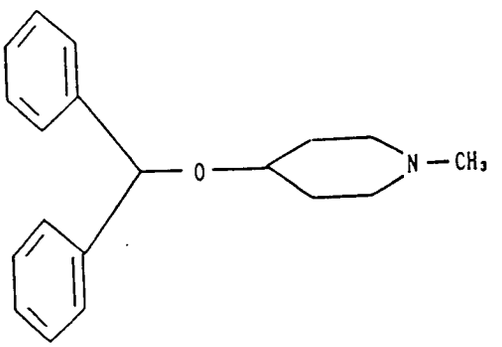
Field of the Invention

The present invention relates to novel piperidine derivatives and pharmacologically acceptable salts thereof which have an antihistaminic and antiallergic activity and are useful for the treatment of, for example, bronchial asthma, allergic rhinitis, dermatosis, and urticaria, and to the method for preparation thereof.

The present invention also relates to a pharmaceutical composition comprising the effective amount of the same.

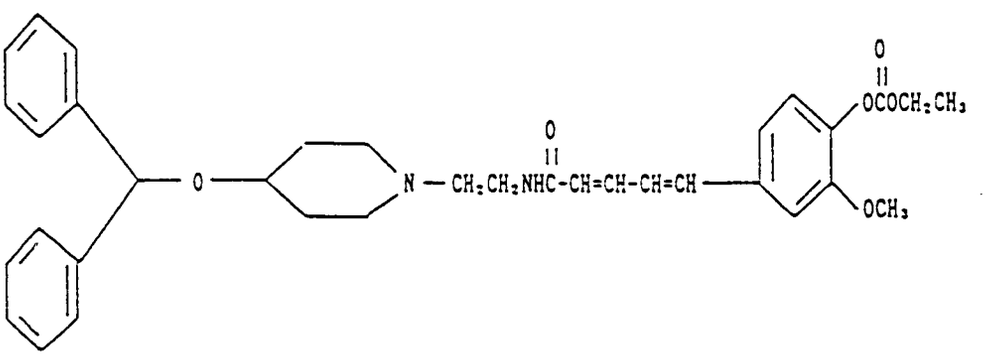
Description of the Prior Art

Among antihistaminic agents having diphenylmethoxypiperidine ring in their molecules, diphenylpyraline (The Merck Index, 11th edition, 3334) represented by the following formula:



has been developed as a clinically available drug and is used for the treatment of such ailments as allergic rhinitis and dermatosis.

Japanese Unexamined Patent Publication No. 228059/1987 discloses TMK-688 (N-[2-[4-(diphenylmethoxy)piperidino]ethyl]-5-[4-(ethoxycarbonyloxy)-3-methoxyphenyl]-2,4-pentadienoylamide) represented by the following formula:



Reference JP-A-61254559 describes a vinyl derivating and 5-lipoxigenase inhibitor used as antiallergic agent.

EP-A-0 226 516 discloses amide derivatives and antiallergic agents containing the same.

EP-A-0 134 124 describes piperidine derivatives and pharmacologically acceptable salts thereof which possess potent selective Histamine H_1-receptor blocking and calcium antagonist properties and are of interest in the treatment of a variety of respiratory, allergenic and cardiovascular disease states.

EP-A-0 335 586 discloses piperidine and piperazine derivatives, process for preparing the same and pharmaceutical compositions containing the same. The compounds are used as antihistaminic and antiallerg-

gic pharmaceutical compositions.

However, neither of the above discloses the compounds of the present invention.

A large number of antihistaminic agents have been developed so far and are used for the treatment of, for example, allergic dermatosis or rhinitis. However, adverse reactions of a central inhibitory action caused by the administration of the known antihistaminic agent such as sleepiness or sedation is found to be a great problem with these known agents. In addition, an anticholinergic action which is considered to be one of the possible reasons for hydrodipsia or mydriasis is another undesired adverse reaction of the antihistaminic agents. Various kinds of research have been conducted to solve the above problems, however, presently available antihistaminic agents are insufficient from a clinical point of view.

SUMMARY OF THE INVENTION

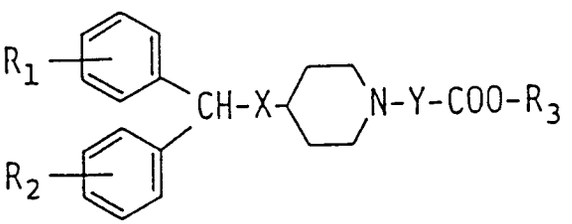
An object of the present invention is to provide novel compounds having an excellent antihistaminic activity as well as excellent antiallergic activity.

Another object of the present invention is to provide novel compounds which extensively eliminate undesired adverse reactions such as a central inhibitory action when administered for the treatment of such ailments as bronchial asthma, allergic rhinitis, dermatosis and urticaria.

A further object of the present invention is to provide a method for preparation of the above novel compounds. Yet another object is to provide a pharmaceutical composition comprising the novel compounds which is useful for the treatment of such ailments as bronchial asthma, allergic rhinitis, dermatosis and urticaria.

The inventors of the present invention have conducted various studies to achieve the foregoing objects and found that the objects can be effectively attained by providing novel piperidine derivatives of the present invention. These derivatives have potent antihistaminic and antiallergic activity and induce few adverse reactions such as central inhibition.

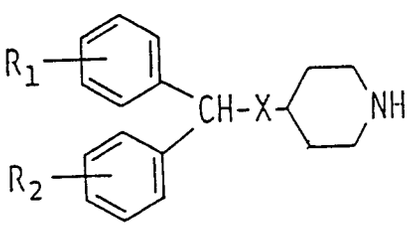
In accordance with the above objects, the present invention provides a piperidine derivative represented by the following general formula (I):



(I)

wherein R_1 and R_2 are the same or different and each independently represents a hydrogen atom, a halogen atom, a C_1 - C_4 alkyl group, or a C_1 - C_4 alkoxy group; R_3 represents a hydrogen atom; X represents an oxygen atom or a sulfur atom; Y represents an alkylene group having 1 to 4 carbon atoms which may be optionally substituted with a C_1 - C_4 alkyl group, or Y represents an -A-O-B-group wherein A and B are the same or different and each independently represents an alkylene group having 1 to 3 carbon atoms which may be optionally substituted with a C_1 - C_4 alkyl group, and pharmacologically acceptable salts of the above compounds.

In accordance with another embodiment of the present invention. the present invention provides a process for preparing a piperidine derivative represented by the general formula (I). The process comprises the steps of reacting a piperidine derivative represented by the following general formula (II):



(II)

wherein R_1, R_2, and X are the same as those defined above,
with a compound represented by Z-Y-COO-R_3 (IIIa) or CH_2 = CHCOO-R_3 (IIIb) wherein R_3 and Y are the same as those defined above, and Z represents a halogen atom, in a solvent or without a solvent, and in the presence or absence of a base, followed by the step of hydrolysis in a solvent using an acid or a base, if necessary.

In accordance with yet another embodiment, the present invention provides an antihistaminic and antiallergic agent comprising an effective amount of a piperidine derivative represented by general formula (I) or the compounds (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (-)-4-[(4-methylphenyl)-phenylmethoxy]-1-piperidinecaproic acid.

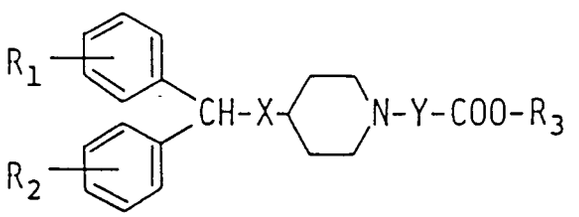
In accordance with a further embodiment, the present invention provides a pharmaceutical composition for treatment of an allergic disease comprising an effective amount of a compound represented by general formula (I) or the compounds (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid.

The invention also provides the use of the piperidine derivative represented by general formula (I) or the compounds (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-methoxyphenyl)-phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, a pharmacologically acceptable salt of the above compounds, an antihistaminic and antiallergic agent comprising the same, or a pharmaceutical composition comprising the same.

Further objects, features and advantages of the present invention will become apparent from the Description of the preferred Embodiments which follows, when read in light of the attached Examples.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a piperidine derivative represented by the following general formula (I):



(I)

wherein R_1 and R_2 are the same or different and each independently represents a hydrogen atom, a halogen atom, a C_1 - C_4 alkyl group, or a C_1 - C_4 alkoxy group; R_3 represents a hydrogen atom; X represents an oxygen atom or a sulfur atom; Y represents an alkylene group having 1 to 4 carbon atoms which may be optionally substituted with a C_1 - C_4 alkyl group, or Y represents an -A-O-B-group wherein A and B are the same or different and each independently represents an alkylene group having 1 to 3 carbon atoms which may be optionally substituted with a C_1 - C_4 alkyl group. The present invention also provides pharmacologically acceptable salts of the above compounds. In addition, the present invention provides a process for preparing the compounds of the general formula (I), and a phrmaceutical composition comprising an effective amount of the same together with a pharmaceutically acceptable carrier or coating.

In the above general formula (I), the halogen atom represented by R_1 and R_2 may be, for example, a fluorine atom, a chlorine atom, or bromine atom, the C_1 - C_4 alkoxy group may be, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, or isobutoxy group, the C_1 - C_4 alkyl group represented by R_1, R_2, and R_3 or the C_1 - C_4 alkyl group which may be a substituent of the alkylene group represented by Y, A, or B may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, or tert-butyl group. The alkylene group having 1 to 4 carbon atoms represented by Y may be substituted with a C_1 - C_4 alkyl group.

Preferred examples of the present invention include:
(±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid;
4-(diphenylmethoxy)-1-piperidinepropionic acid;
(±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinepropionic acid;
(±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinebutyric acid;

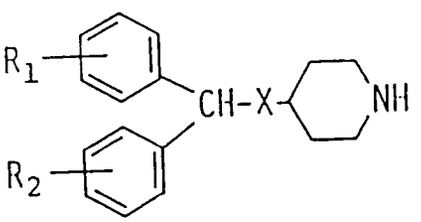
(±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinevaleric acid;
(±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid;
(±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinepropionic acid;
(±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinebutyric acid;
(±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid;
(±)-4-[(2-chlorophenyl)phenylmethoxy]-1-piperidinebutyric acid;
(±)-4-[(4-fluorophenyl)phenylmethoxy]-1-piperidinebutyric acid;
(±)-4-[(4-fluorophenyl)phenylmethoxy]-1-piperidinevaleric acid;
4-[bis(4-fluorophenyl)methoxy]-1-piperidinevaleric acid;
(+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid;
(-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid;
(+)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid;
(-)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid;
(+)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid;
(-)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid;
4-[bis(4-fluorophenyl) methoxy]-1-piperidinevaleric acid;

The compound of the present invention represented by the above general formula (I) or the compounds (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid may be converted to pharmacologically acceptable salts, If desired, and may then be reconverted to produce the free compound from the obtained salts.

The pharmacologically acceptable salts of the compounds of the present invention represented by the general formula (I) or the compounds (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid may be acid addition salts or alkali addition salts. Examples of the acid addition salts include mineral acids such as for example hydrochloride, hydrobromide, sulfate, nitrate, and phosphate, and organic acid salt such as for example acetate, maleate, fumarate, malate, citrate, oxalate, lactate, and tartrate. Examples of the alkali addition salts include metal salts such as for example sodium, potassium, and calcium salt, and organic alkali salts such as for example ammonium salts, methylamine, ethylamine, dimethylamine, triethylamine, ethanolamine, piperidine, and piperazine salts.

The compound of the present invention represented by the above general formula (I) or the compounds (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid may have one or more asymmetric carbon atoms in the molecule, and consequently, optically active compounds and diastereoisomers may exist, which are incorporated within the scope of the present invention.

The novel piperidine derivatives of the present invention represented by the above general formula (I) or the compounds (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-methoxyphenyl)-phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid can be prepared by reacting a piperidine derivative represented by the following general formula (II):



(II)

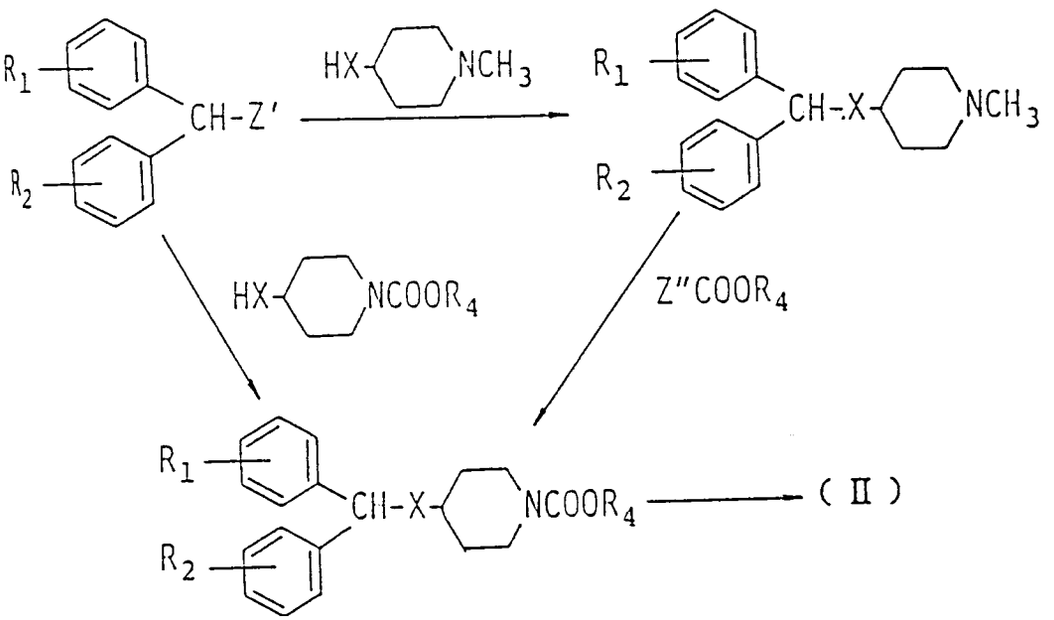
wherein R_1, R_2, and X are the same as those defined above, with a compound represented by Z-Y-COO-R_3 (IIIa) or CH_2 = CHCOO-R_3 (IIIb) wherein R_3 and Y are the same as those defined above, and Z represents a halogen atom, in a solvent or without a solvent in the presence or absence of a base, and followed by hydrolysis in a solvent by using an acid or a base, if necessary.

Any inert solvent may be used in the condensation process of the present invention. Examples of the inert solvent include benzene. toluene, tetrahydrofuran, dioxane, acetone, acetonitrile, methanol, ethanol, isopropanol, n-butanol, dimethyl sulfoxide, and N,N-dimethylformamide.

Examples of the base used in the process of the present invention include potassium carbonate, sodium carbonate, pyridine, and triethylamine. The reaction may be carried out at from 0 to 200 °C.

For the hydrolysis process, an acid such as for example hydrochloric acid or sulfuric acid, or a base such as for example sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, or sodium bicarbonate may be used. A solvent used in the hydrolysis may be, for example, water, methanol, ethanol, acetone, or tetrahydrofuran, and the hydrolysis may be carried our at from 0 to 100 °C.

In addition, the compounds represented by the above general formula (II), used as starting materials for the above process, are, with a few exceptions, novel compounds which may be prepared according to the following process:



wherein, R_1, R_2, and X are the same as those defined above, Z' and Z'' are the same or different and each represents a halogen atom, and R_4 represents a lower alkyl group.

The novel piperidine compound of the present invention represented by the above general formula (I) or the compounds (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-methoxyphenyl)-phenylmethoxy]-1-piperidinecaproic acid, (±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid, (-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid and the pharmacologically acceptable salt thereof has an excellent anti-histaminic and antiallergic activity, and thus is quite useful for the treatment of an allergic disease, such as, for example, bronchial asthma, allergic rhinitis, dermatosis, and urticaria.

The piperidine compounds of the present invention and their pharmacologically acceptable salts may be administered orally or parenterally to a patient as a pharmaceutical composition which comprises an effective amount of said compound or said salt together with a pharmaceutically acceptable carrier or coating.

The pharmaceutical composition suitable for oral administration may be, for example, tablet, capsule, powder, subtilized granule, granule, solution, or syrup. The pharmaceutical composition suitable for parenteral administration may be injection, suppository, inhalant, eye drop, nasal drop, ointment, or cataplasm. The pharmaceutically acceptable carrier or coating used for the preparation of the pharmaceutical composition may be excipient, disintegrant or agent for accelerating disintegration, binder, lubricant, coating agent, pigment, diluent, base, solubilizing agent, solubilizer, isotonicity, pH adjusting agent, stabilizer, propellant, and adhesive.

For the preparation of the pharmaceutical composition suitable for oral administration, dermal administration, or mucosal application, the coating or carrier may comprise the following: an excipient such as for example glucose, lactose, D-mannitol, starch, or crystalline cellulose; a disintegrant or an agent for accelerating disintegration such as for example carboxymethylcellulose, starch, or calcium carboxymethylcellulose; a binder such as for example hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, or gelatin; a lubricant such as for example magnesium stearate or talc; a coating agent such as for example hydroxypropylmethylcellulose, sucrose, or titanium oxide; a base such as for example petrolatum, liquid paraffin, polyethyleneglycol, or hard fat; a propellant such as for example fron, diethylether, or compressed gas; an adhesive such as for example sodium polyacrylate, polyvinylalcohol, methylcellulose, polyisobutylene, or polybutene; or a base sheet such as for example cloth or plastic sheet. The pharmaceutical composition suitable for injection may comprise the following: a solubilizing agent or a solubilizer, e.g., distilled water for injection, saline, or propylene glycol which is useful for an aqueous composition or a composition for preparing aqueous solution before use; an isotonicity agent such as for example glucose, sodium chloride, D-mannitol, or glycerin; and a pH adjusting agent such as for example an inorganic or organic acid or an inorganic or organic base.

The dose of the pharmaceutical composition of the present invention for an adult patient may generally be from about 1 to 300 mg per day for oral administration, which may be increased or decreased depending on the conditions of the patient to be treated.

The present invention will be further illustrated by the following Examples and Reference Examples. The Examples are given by way of illustration only and are not to be construed as limiting.

Examples and Reference Examples

The following example shows the excellent effectiveness of the present compounds. The results of 48 hr homologous passive cutaneous anaphylaxis (PCA) in rats with the monitoring of antiallergic activity and potentiation of hexobarbital-induced anesthesia in mice with the monitoring of central nervous depressive activity are summarized in Table 1. The following compounds were used as the reference compounds.

Reference compound A: diphenylpyraline hydrochloride
Reference compound B: TMK-688

1. 48 hr homologous passive cutaneous anaphylaxis (PCA) in rats

a) Preparation of DNP-As and rat anti-DNP-As serum

Ascaris extract coupled with 2,4-dinitrophenyl group (DNP-As) was prepared by the method of Koda et al. (Folia pharmacol. japon., 78, 319-334, 1981) and anti-DNP-As containing IgE antibody serum was prepared by the method of Tada and Okumura (J. Immunol., 106, 1019-1025, 1971). The PCA titer of the antiserum was estimated as 1:128 by 48 hr PCA in rats.

b) 48 hr homologous passive cutaneous anaphylaxis (PCA) in rats

Male Wistar rats weighing 160 to 220 g were sensitized passively by intradermal injection in the back, of 0.05 ml of anti-DNP-As serum, diluted 21-fold with saline. After 48 hr, the animals (18-20 hr fasted) were given i.v. 0.5 ml of 1% Evans blue solution containing 1 mg of DNP-As. After additional thirty minutes, the animals were killed by stunning and the skins were removed. The intensity of the response was evaluated by assaying the amount of dye leaked according to the method of Katayama et al. (Microbiol. Immunol., 22, 89-101, 1978). The percent inhibition of PCA was calculated using the following formula:

$$\text{Percent inhibition} = \frac{\text{Amount of dye leaked of control} - \text{Amount of dye leaked of test ccmpound}}{\text{Amount of dye leaked of control}} \times 100$$

Test compounds were given orally in a dose 1.0 mg/kg 1 hr prior to challenge with antigen. As a control, 5 ml/kg of vehicle (0.5% CMC) alone were given in a similar manner.

The results are shown in Table 1.

2. Potentiation of hexobarbital-induced anesthesia in mice

The loss of righting reflex induced by hexobarbital was used as an index of anesthesia. Groups of eight male ddY mice (20-24 hr fasted) weighing 19 to 27 g were treated orally with the test compounds (30 mg/kg) or vehicle. thirty minutes later, 80 mg/kg of hexobarbital sodium were injected i.p. to the animals and the duration of loss of righting reflex was observed. The percent increase of sleeping time was calculated using the following formula:

$$\text{Persent increase} = \frac{\text{Sleeping time of test compound} - \text{Sleeping time of control}}{\text{Sleeping time of control}} \times 100$$

The results are listed in Table 1.

Table 1

Test compound	the percent inhibition of PCA in rats (%, 1 mg/kg, p.o.)	the percent increase of hexobarbital-induced anesthesia in mice (%, 30 mg/kg, p.o.)
Example 1	68	-8
Example 2	62	29
Example 7	51	-2
Example 8	65	3
Example 9	63	12
Example 12	68	24
Example 17	60	4
Example 18	54	18
Example 20	71	20
Example 34	53	29
Example 37	73	21
Example 38	83	31
Example 41	64	-12
Example 45	55	29
Example 46.	36	-1
Reference compound A	-1	75
Reference compound B	8	35

The present compounds exhibited a more potent antiallergic activity and less potent central nervous depressive activity than the reference compounds.

Reference 1

(±)-4-[(4-Fluorophenyl)phenylmethoxy]-1-methylpiperidine hydrochloride

A mixture of 48.6 g of 4-fluorobenzhydryl chloride, 25.3 g of 4-hydroxy-1-methylpiperidine and 18.3 g of potassium carbonate was heated with stirring at 140 °C for 5.5 hours. After cooling, water was added to the reaction mixture and extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was taken up in ether and the organic layer was extracted with hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate and extracted with ether. The extract was washed with water. dried and concentrated to give 53.3 g of reddish brown liquid, which was converted to the hydrochloride in the usual manner and then recrystallized from a mixture of ethanol and ether to give colorless needles, mp 192 - 193 °C.

Analysis for $C_{19}H_{22}FNO \cdot HCl \cdot 1/4H_2O$:			
Calculated	C, 67.05;	H, 6.96;	N, 4.12
Found	C, 67.13;	H, 6.89;	N, 4.08

Reference 2

4-(Diphenylmethylthio)-1-methylpiperidine hydrochloride

A mixture of 12.7 g of benzhydryl chloride, 8.20 g of 4-mercapto-1-methylpiperidine and 8.64 g of potassium carbonate was heated with stirring at 150 °C for 3.5 hours. After cooling, water was added to the reaction mixture and extracted with benzene. The benzene layer was extracted with hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate and extracted with ether. The extract was washed with water, dried and concentrated to give 10.3 g of brown liquid, which was purified by column chromatography on silica gel [eluent: chloroform-methanol (50:1)] to give an oily residue. The residue was solidified with n-hexane to give 6.41 g of pale brown crystals, m.p. 72 ~ 74 °C , which were converted to the hydrochloride in the usual manner and then recrystallized from a mixture of acetone and ether to give pale yellow needles, mp 182 ~ 183 °C.

Analysis for $C_{19}H_{23}NS \cdot HCl$:			
Calculated	C, 68.34;	H, 7.24;	N, 4.19
Found	C, 68.21;	H, 7.05;	N, 4.18

The compounds of References 3 to 12 were prepared in the same manner as described in References 1 and 2.

Reference 3

(±)-4-[(2-chlorophenyl)phenylmethoxy]-1-methylpiperidine fumarate

Colorless crystals, mp 156 ~ 157 °C (EtOH-Et_2O).

Analysis for $C_{19}H_{22}ClNO \cdot C_4H_4O_4$:			
Calculated	C, 63.96;	H, 6.07;	N, 3.24
Found	C, 63.97;	H, 6.04;	N, 3.27

Reference 4

(±)-4-[(3-Chlorophenyl)phenylmethoxy]-1-methylpiperidine fumarate

Colorless prisms, mp 148 ~ 150 °C (EtOH-Et_2O).

Analysis for $C_{19}H_{22}ClNO \cdot C_4H_4O_4$:			
Calculated	C, 63.96;	H, 6.07;	N, 3.24
Found	C, 63.90;	H, 6.17;	N, 3.20

Reference 5

(±)-1-Methyl-4-[(4-methylphenyl)phenylmethoxy]piperidine maleate

Colorless needles, mp 132 ~ 133 °C (EtOH-Et_2O).

Analysis for $C_{20}H_{25}NO \cdot C_4H_4O_4$:			
Calculated	C, 70.05;	H, 7.10;	N, 3.40
Found	C, 69.85;	H, 7.06;	N, 3.48

Reference 6

4-[Bis(4-fluorophenyl)methoxy]-1-methylpiperidine fumarate

Colorless needles, mp 147 ~ 148 °C (EtOH-Et_2O).

Analysis for $C_{19}H_{21}F_2NO \cdot C_4H_4O_4$:			
Calculated	C, 63.73;	H, 5.81;	N, 3.23
Found	C, 63.77;	H, 5.83;	N, 3.22

Reference 7

(±)-4-[(4-Ethylphenyl)phenylmethoxy]-1-methylpiperidine fumarate

Colorless crystals, mp 171 ~ 174 °C (EtOH-Et_2O).

Analysis for $C_{21}H_{27}NO \cdot C_4H_4O_4$:			
Calculated	C, 70.57;	H, 7.34;	N, 3.29
Found	C, 70.48;	H, 7.22;	N, 3.23

Reference 8

(±)-1-Methyl-4-[(4-n-propylphenyl)phenylmethoxy]piperidine hydrochloride

Colorless crystals, mp 166 ~ 169 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{29}NO \cdot HCl \cdot H_2O$:			
Calculated	C, 69.91;	H, 8.53;	N, 3.71
Found	C, 70.12;	H, 8.33;	N, 3.66

Reference 9

(±)-4-[(4-n-Butylphenyl)phenylmethoxy]-1-methylpiperidine fumarate

Colorless crystals, mp 96 ~ 98 °C (AcOEt).

Analysis for $C_{23}H_{31}NO \cdot C_4H_4O_4$:			
Calculated	C, 71.50;	H, 7.78;	N, 3.09
Found	C, 71.20;	H, 7.98;	N, 3.18

Reference 10

(±)-4-[(4-tert-Butylphenyl)phenylmethoxy]-1-methylpiperidine hydrochloride

Colorless crystals, mp 212 ~ 215 °C (EtOH-AcOEt).

Analysis for $C_{23}H_{31}NO \cdot HCl$:			
Calculated	C, 73.87;	H, 8.62;	N, 3.75
Found	C, 73.76;	H, 8.65;	N, 3.73

Referecne 11

4-[Bis(4-methylphenyl)methoxy]-1-methylpiperidine fumarate

Colorless crystals, mp 135 ~ 137 °C (Me_2CO).

Analysis for $C_{21}H_{27}NO \cdot C_4H_4O_4$:			
Calculated	C, 70.57;	H, 7.34;	N, 3.29
Found	C, 70.39;	H, 7.35;	N, 3.38

Reference 12

(±)-4-[4-Ethoxyphenyl)phenylmethoxy]-1-methylpiperidine fumarate

Colorless needles, mp 164 ~ 165.5 °C (EtOH).

Analysis for $C_{21}H_{27}NO_2 \cdot C_4H_4O_4$:			
Calculated	C, 68.01;	H, 7.08;	N, 3.17
Found	C, 67.83;	H, 7.28;	N, 3.08

Reference 13

(±)-Ethyl 4-[(4-fluorophenyl)phenylmethoxy]-1-piperidinecarboxylate

A quantity of 92.9 g of ethyl chlorocarbonate was added dropwise to a solution of 50.2 g of (±)-4-[(4-fluorophenyl)phenylmethoxy]-1-methylpiperidine in 200 ml of toluene, and the resulting solution was refluxed for 8 hours. After cooling, the reaction soltuion was washed with hydrochloric acid and water, dried and concentrated to give 51.9 g of yellowish brown liquid.

Mass spectrum m/z:	357 (M^+).
IR spectrum ν (liq)cm^{-1} :	1698 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	1.24 (3H, t, J = 7Hz), 1.54-1.96 (4H, m), 3.00 - 3.36 (2H, m), 3.40 - 3.94 (3H, m), 4.11 (2H, q, J = 7Hz), 5.50 (1H, s), 6.97 (2H, t, J = 9Hz), 7.15 - 7.50 (7H, m).

Reference 14

Ethyl 4-(diphenylmethylthio)-1-piperidinecarboxylate

A quantity of 11.6 g of ethyl chlorocarbonate was added dropwise to a solution of 6.40 g of 4-(diphenylmethylthio)-1-methylpiperidine in 30 ml of toluene, and then the resulting mixture was refluxed for 2.5 hours. After cooling, the reaction mixture was washed with hydrochloric acid and water, dried and concentrated to give 7.73 g of pale yellowish brown solid, which were recrystallized from n-hexane to give colorless needles, mp 70 ~ 71 °C.

Analysis for $C_{21}H_{25}NO_2S$:			
Calculated	C, 70.95;	H, 7.09;	N, 3.94
Found	C, 71.09;	H, 6.89;	N, 3.92

The compounds of References 15 to 25 were prepared in the same manner as described in References 13 and 14.

Reference 15

(±)-Ethyl 4-[(2-chlorophenyl)phenylmethoxy]-1-piperidinecarboxylate

Pale brown liquid.

Mass spectrum m/z:	373, 375 (3:1, M^+).
IR spectrum ν (liq)cm^{-1} :	1700 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	1.24(3H, t, J = 7Hz), 1.40 - 2.10 (4H, m), 3.00 - 4.00 (5H, m), 4.11 (2H, q, J = 7 Hz), 5.99 (1H, s), 7.00 - 7.70 (9H, m).

Reference 16

(±)-Ethyl 4-[(3-chlorophenyl)phenylmethoxy]-1-piperidinecarboxylate

Pale brown liquid.

Mass spectrum m/z:	373, 375 (3:1, M^+).
IR spectrum ν (liq) cm^{-1} :	1698 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	1.25 (3H, t, J = 7Hz), 1.50 - 2.05 (4H, m), 3.00 - 4.00 (5H, m), 4.12 (2H, q, J = 7Hz), 5.47 (1H, s), 7.00 - 7.55 (9H, m).

Reference 17

(±)-Ethyl 4-[(4-chlorophenyl)phenylmethoxy]-1-piperidinecarboxylate

Pale yellow liquid.

Mass spectrum m/z:	373, 375 (3:1, M^+).
IR spectrum ν (liq) cm^{-1} :	1698 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	1.24 (3H, t, J = 7Hz), 1.45 - 2.00 (4H, m), 3.00 - 3.95 (5H, m), 4.11 (2H, q, J = 7Hz), 5.48 (1H, s), 7.10 - 7.50 (9H, m).

Reference 18

(±)-Ethyl 4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecarboxylate

Pale yellowish brown liquid.

Mass spectrum m/z:	353(M^+).
IR spectrum ν (liq) cm^{-1} :	1700 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	1.24 (3H, t, J = 7Hz), 1.40 - 2.00 (4H, m), 2.31 (3H, s), 3.00 - 3.96 (5H, m), 4.11 (2H, q, J = 7Hz), 5.49 (1H, s), 7.00 - 7.50 (9H, m).

Reference 19

(±)-Ethyl 4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecarboxylate Pale brown liquid.

Mass spectrum m/z:	369(M^+).
IR spectrum ν (liq) cm^{-1} :	1696 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	1.24 (3H, t, J = 7Hz), 1.50 - 2.00 (4H, m), 3.00 - 3.95 (5H, m), 3.77 (3H, s), 4.11 (2H, q, J = 7Hz), 5.48 (1H, s), 6.84 (2H, d, J = 9Hz), 7.10 - 7.50 (5H, m), 7.24 (2H, d, J = 9Hz).

Reference 20

(±)-Ethyl 4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecarboxylate

Pale brown liquid.

Mass spectrum m/z:	367(M^+).
IR spectrum ν (liq) cm^{-1} :	1700 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	1.21 (3H, t, J = 7Hz), 1.24 (3H, t, J = 7Hz), 1.55 - 2.04 (4H, m), 2.62 (2H, q, J = 7Hz), 3.00 - 3.97 (5H, m), 4.11 (2H, q, J = 7Hz), 5.50 (1H, s), 7.00 - 7.50 (9H, m).

Reference 21

(±)-Ethyl 4-[(4-n-propylphenyl)phenylmethoxy]-1-piperidinecarboxylate

Yellow liquid.

Mass spectrum m/z:	381(M^+).
IR spectrum ν (liq) cm^{-1} :	1702 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	0.92 (3H, t, J = 7Hz), 1.24 (3H, t, J = 7Hz), 1.36 - 2.04 (6H, m), 2.55 (2H, t, J = 7Hz), 3.00 - 3.96 (5H, m), 4.11 (2H, q, J = 7Hz), 5.49 (1H, s), 7.00 - 7.46 (9H, m).

Reference 22

(±)-Ethyl 4-[(4-n-butylphenyl)phenylmethoxy]-1-piperidinecarboxylate

Yellow liquid.

Mass spectrum m/z:	395(M^+).
IR spectrum ν (liq) cm^{-1} :	1702 (COO-).
NMR spectrum δ ($CDCl_3$)ppm:	0.91 (3H, t, J = 7Hz), 1.24 (3H, t, J = 7Hz), 1.09 - 2.02 (8H, m), 2.57 (2H, t, J = 7Hz), 3.04 - 3.96 (5H, m), 4.11 (2H, q, J = 7Hz), 5.49 (1H, s), 7.04 - 7.46 (9H, m).

Reference 23

(±)-Ethyl 4-[(4-tert-butylphenyl)phenylmethoxy]-1-piperidinecarboxylate

Yellow liquid.

Mass spectrum m/z:	395(M^+).
IR spectrum ν (liq) cm^{-1} :	1702 (COO-).
NMR spectrum δ ($CDCl_3$) ppm:	1.24 (3H, t, J = 7Hz), 1.29 (9H, s), 1.50 - 1.90 (4H, m), 3.00 - 3.96 (5H, m) , 4.11 (2H, q, J = 7Hz), 5.50 (1H, s), 7.10 - 7.46 (9H, m).

Reference 24

Ethyl 4-[bis(4-methylphenyl)methoxy]-1-piperidinecarboxylate

Orange liquid.

Mass spectrum m/z:	367(M^+).
IR spectrum ν (liq) cm^{-1} :	1700 (COO-).
NMR spectrum δ ($CDCl_3$) ppm:	1.24 (3H, t, J = 7Hz), 1.39 - 2.00 (4H, m), 2.31 (6H, s), 2.98 - 3.95 (5H, m). 4.11 (2H, q, J = 7Hz), 5.46 (1H, s), 7.00 - 7.37 (8H, m).

Reference 25

(±)-Ethyl 4-[(4-ethoxyphenyl)phenylmethoxy]-1-piperidinecarboxylate

Pale brown liquid.

Mass spectrum m/z:	383(M^+).
IR spectrum ν (liq) cm^{-1} :	1700 (COO-).
NMR spectrum δ ($CDCl_3$) ppm:	1.24 (3H, t, J = 7Hz), 1.39 (3H, t, J = 7Hz), 1.54 - 2.00 (4H, m), 3.01 - 3.88 (5H, m), 4.01 (2H, q, J = 7Hz), 4.12 (2H, q, J = 7Hz), 5.47 (1H, s), 6.83 (2H, d, J = 9Hz), 7.08 - 7.47 (5H, m), 7.22 (2H, d, J = 9Hz).

Reference 26

(±)-4-[(4-Fluorophenyl)phenylmethoxy]piperidine hydrochloride

A mixture of 51.4 g of (±)-ethyl 4-[(4-fluorophenyl)phenylmethoxy]-1-piperidinecarboxylate, 50.0 g of sodium hydroxide, 52.5 ml of water and 300 ml of ethanol was refluxed for 22 hours and concentrated. Water was added to the residue and extracted with ether. The ether layer was washed with water and extracted with hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate and extracted with ether. The extract was washed with water, dried and concentrated to give 38.3 g of pale yellowish brown liquid, which was converted to the hydrochloride in the usual manner and then recrystallized from a mixture of ethanol and ether to give colorless needles, mp 173 ~ 174 °C.

Analysis for $C_{18}H_{20}FNO \cdot HCl$:			
Calculated	C, 67.18;	H, 6.58;	N, 4.35
Found	C, 67.19;	H, 6.53;	N, 4.32

Reference 27

4-(Diphenylmethylthio)piperidine hydrochloride

A mixture of 7.60 g of ethyl 4-(diphenylmethylthio)-1-piperidinecarboxylate, 5.12 g of sodium hydroxide, 12.8 ml of water and 50 ml of ethanol was refluxed for 13 hours and then concentrated. Water was added to the residue and the resulting mixture was extracted with ether. The ether layer was extracted with hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was washed with water, dried and concentrated to give 5.05 g of pale brown crystals,

mp 86 ~ 88 °C . The crystals were converted to the hydrochloride in the usual manner and then recrystallized from ethanol to give pale yellow prisms. mp 199~ 200 °C.

Analysis for $C_{18}H_{21}NS \cdot HCl$:			
Calculated	C, 67.58;	H, 6.93;	N, 4.38
Found	C, 67.55;	H, 6.79;	N, 4.34

The compounds of References 28 to 38 were prepared in the same manner described in References 26 and 27.

Reference 28

(±)-4-[(2-Chlorophenyl)phenylmethoxy]piperidine hydrochloride

Colorless crystals, mp 157 ~ 160 °C (EtOH-Et_2O).

Analysis for $C_{18}H_{20}ClNO \cdot HCl$:			
Calculated	C, 63.91;	H, 6.26;	N, 4.14
Found	C, 63.69;	H, 6.21;	N, 4.12

Reference 29

(±)-4-[(3-Chlorophenyl)phenylmethoxy]piperidine fumarate

Colorless crystals, mp 159 ~ 160 °C (MeOH-Et_2O).

Analysis for $C_{18}H_{20}ClNO \cdot C_4H_4O_4$:			
Calculated	C, 63.23;	H, 5.79;	N, 3.35
Found	C, 63.16;	H, 5.70;	N, 3.33

Reference 30

(±)-4-[4-Chlorophenyl)phenylmethoxy]piperidine maleate

Colorless prisms, mp 159 ~ 161 °C (EtOH).

Analysis for $C_{18}H_{20}ClNO \cdot C_4H_4O_4$:			
Calculated	C, 63.23;	H, 5.79;	N, 3.35
Found	C, 63.07;	H, 5.89;	N, 3.39

Reference 31

(±)-4-[(4-Methylphenyl)phenylmethoxy]piperidine fumarate

Colorless needles, mp. 188~ 189 °C (EtOH).

Analysis for $C_{19}H_{23}NO \cdot C_4H_4O_4$:			
Calculated	C, 69.50;	H, 6.85;	N, 3.52
Found	C, 69.34;	H, 7.02;	N, 3.57

Reference 32

(±)-4-[(4-Methoxyphenyl)phenylmethoxy]piperidine fumarate

Colorless crystals, mp 152 ~ 153 °C (EtOH-Et_2O).

Analysis for $C_{19}H_{23}NO_2 \cdot C_4H_4O_4 \cdot 1/4H_2O$:			
Calculated	C, 66.09;	H, 6.63;	N, 3.35
Found	C, 66.06;	H, 6.45;	N, 3.42

Reference 33

(±)-4-[(4-Ethylphenyl)phenylmethoxy]piperidine fumarate

Colorless crystals, mp 127 ~ 129 °C (EtOH-Et_2O).

Analysis for $C_{20}H_{25}NO \cdot C_4H_4O_4$:			
Calculated	C, 70.05;	H, 7.10;	N, 3.40
Found	C, 70.33;	H, 7.10;	N, 3.43

Reference 34

(±)-4-[(4-n-Propylphenyl)phenylmethoxy]piperidine fumarate

Colorless needles, mp 142 ~ 143.5 °C (EtOH-Et_2O).

Analysis for $C_{21}H_{27}NO \cdot C_4H_4O_4$:			
Calculated	C, 70.57;	H, 7.34;	N, 3.29
Found	C, 70.62;	H, 7.44;	N, 3.32

Reference 35

(±)-4-[(4-n-Butylphenyl)phenylmethoxy]piperidine fumarate

Colorless pillars, mp 183 ~ 184 °C (MeOH-Et_2O).

Analysis for $C_{22}H_{29}NO \cdot 1/2C_4H_4O_4$:			
Calculated	C, 75.56;	H, 8.19;	N, 3.67
Found	C, 75.39;	H, 8.26;	N, 3.56

Reference 36

(±)-4-[(4-tert-Butylphenyl)phenylmethoxy]piperidine fumarate

Colorless crystals, mp 163 ~ 166 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{29}NO \cdot C_4H_4O_4$:			
Calculated	C, 71.05;	H, 7.57;	N, 3.19
Found	C, 70.99;	H, 7.52;	N, 3.23

Reference 37

4-[Bis(4-methylphenyl)methoxy]piperidine fumarate

Colorless needles, mp 164 ~ 168 °C (MeOH).

Analysis for $C_{20}H_{25}NO \cdot C_4H_4O_4$:			
Calculated	C, 70.05;	H, 7.10;	N, 3.40
Found	C, 69.93;	H, 7.16;	N, 3.31

Reference 38

(±)-4-[(4-Ethoxyphenyl)phenylmethoxy]piperidine fumarate

Colorless prisms, mp 112 ~ 115 °C (EtOH).

Analysis for $C_{20}H_{25}NO \cdot C_4H_4O_4$:			
Calculated	C, 67.43;	H, 6.84	N, 3.28
Found	C, 67.24;	H, 6.85;	N, 3.33

Reference 39

(+)- and (-)-4-[(4-methylphenyl)phenylmethoxy]piperidine

(+)-Dibenzoyl-D-tartaric acid (19.3 g) was added to a solution of 25.3 g of (±)-4-[(4-methylphenyl)-phenylmethoxy]piperidine in methanol. The precipitate was collected by filtration to give 15.8 g of the crude (+)-dibenzoyl-D-tartarate. The mother liquor was concentrated and the residue obtained was converted to the free base in the usual manner. (-)-Dibenzoyl-L-tartaric acid (8.28 g) was added to the solution of the free

base in methanol. The precipitate was collected by filtration to give 16.8 g of the crude (-)-dibenzoyl-L-tartarate. The crude (+)-dibenzoyl-D-tartarate was recrystallized from methanol to give 6.72 g of the pure (+)-dibenzoyl-D-tartarate as colorless needles, mp 166.5~ 167 °C . The needles were converted to the free base in the usual manner to give 3.73 g of (+)-4-[(4-methylphenyl)phenylmethoxy]piperidine as colorless liquid [specific rotation $[\alpha]_D^{20}$ + 13.3 ° (c = 0.5, $CHCl_3$), optical purity 96% ee]. The free base was converted to the fumarate in the usual manner, and the fumarate was recrystallized from ethanol to give colorless needles, mp 173 ~ 174 °C.
specific rotation $[\alpha]_D^{20}$ + 10.2 ° (c = 0.5, MeOH).

Analysis for $C_{19}H_{23}NO \cdot C_4H_4O_4$:			
Calculated	C, 69.50;	H, 6.85;	N, 3.52
Found	C, 69.53;	H, 6.93;	N, 3.56

The crude (-)-dibenzoyl-L-tartarate was recrystallized from methanol to give 9.37 g of the pure (-)-dibenzoyl-L-tartarate as colorless needles, mp 169 °C . The needles were converted to the free base in the usual manner to give 5.16 g of (-)-4-[(4-methylphenyl)phenylmethoxy]piperidine as a colorless liquid [specific rotation $[\alpha]_D^{20}$ -13.4 ° (c = 0.5, $CNCl_3$), optical purity 96% ee]. The free base was converted to the fumarate in the usual manner, and the fumarate was recrystallized from ethanol to give colorless needles, mp 173.5 ~ 175 °C.
specific rotation $[\alpha]_D^{20}$ -10.1 ° (c = 0.5, MeOH).

Analysis for $C_{19}H_{23}NO \cdot C_4H_4O_4$:			
Calculated	C, 69.50;	H, 6.85;	N, 3.52
Found	C, 69.62;	H, 6.95;	N, 3.60

Reference 40

(±)-Methyl 4[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproate hydrochloride

A mixture of 7.00 g of (±)-4-[(4-methylphenyl)phenylmethoxy]piperidine,6.25 g of methyl 6-bromocaproate, 3.44 g of potassium carbonate and 35 ml of N,N-dimethylformamide was stirred at 70 °C for 3.5 hours. After cooling, water was added to the reaction mixture and the resulting mixture was extracted with ether. The ether layer was extracted with hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate and extracted with ether. The extract was washed with water, dried and concentrated to give 8.96 g of yellow liquid. The yellow liquid was converted to the hydrochloride in the usual manner to give 8.29 g of pale orange crystals, which were then recrystallised from ethyl acetate to give colorless needles, mp 126~ 129 °C.

Analysis for $C_{26}H_{35}NO_3 \cdot HCl$:			
Calculated	C, 70.01;	H, 8.14;	N, 3.14
Found	C, 69.78;	H, 8.13;	N, 3.14

Reference 41

Ethyl 4-(diphenylmethoxy)-1-piperidinepropionate hydrochloride

A mixture of 5.34 g of 4-(diphenylmethoxy)piperidine, 3.98 g of ethyl 3-bromopropionate, 2.76 g of potassium carbonate and 30 ml of N,N-dimethylformamide was stirred at 70 °C for 3 hours. After cooling, water was added to the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried and concentrated to give 5.90 g of pale yellow liquid. The yellow liquid was converted to the hydrochloride in the usual manner, and the hydrochloride was then recrystallized from ethanol to give colorless plates, mp 176 ~ 178 °C.

Analysis for $C_{23}H_{29}NO_3 \cdot HCl$:			
Calculated	C, 68.39;	H, 7.49;	N, 3.47
Found	C, 68.29;	H, 7.33;	N, 3.45

Reference 42

Ethyl 4-[bis(4-methylphenyl)methoxy]-1-piperidinepropionatehydrochloride

A mixture of 3.25 g of 4-[bis(4-methylphenyl)methoxy]-piperidine 1.43 g of ethyl acrylate and 20 ml of ethanol was refluxed for 2 hours and then concentrated. The residue was dissolved in ether and made acidic with ethanolic hydrogen chloride give 4.23 g of colorless crystals. The crystals were recrystallized from a mixture of acetone and ether to give colorless needles, mp 153 ~ 156 °C.

Analysis for $C_{25}H_{33}NO_3 \cdot HCl$:			
Calculated	C, 69.51;	H, 7.93;	N, 3.24
Found	C, 69.39;	H, 7.96;	N, 3.25

Reference 43

Ethyl 4-(diphenylmethylthio)-1-piperidinepropionate hydrochloride

A mixture of 1.70 g of 4-(diphenylmethylthio)piperidine, 1.30 g of ethyl 3-bromopropionate, 0.83 g of potassium carbonate and 10 ml of N,N-dimethylformamide was stirred at 70 °C for 3 hours. After cooling, water was added to the reaction mixture and the resulting mixture was extracted with ether. The ether layer was extracted with hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate and extracted with ether. The extract was washed with water, dried and concentrated to give 1.98g of pale yellowish brown liquid. The brown liquid was converted to the hydrochloride and then recrystallized from a mixture of ethanol and ether to give colorless crystals, mp 149~ 150 °C.

Analysis for $C_{23}H_{29}NO_2S \cdot HCl$:			
Calculated	C, 65.77;	H, 7.20;	N, 3.33
Found	C, 63.72;	H, 7.06;	N, 3.36

Reference 44

(±)-Methyl 2-[4-[(4-fluorophenyl)phenylmethoxy]piperidino]ethoxyacetate

A mixture of 4.46 g of (±)-[(4-fluorophenyl)-phenylmethoxy]piperidine, 2.75 g of methyl 2-chloroethoxyacetate, 2.07 g of potassium carbonate and 45 ml of N,N-dimethylformamide was stirred at 70 °C for 22 hours. After cooling, water was added to the reaction mixture and extracted with ether. The extract was washed with water, dried and evaporated. The residue was purified by column chromatography on silica gel [eluent: chloroform-methanol(50:1)] to give 4.40 g of yellowish orange liquid.

Mass spectrum m/z: 401 (M^+).

IR spectrum ν (liq) cm^{-1}: 1758 (COO-).

NMR spectrum δ ($CDCl_3$) ppm: 1.60 - 2.00 (4H, m), 2.00 - 3.00 (4H, m), 2.60 (2H, t, J = 5.5Hz), 3.20 - 3.55 (1H, m), 3.66 (2H, t, J = 5.5 Hz), 3.73 (3H, s), 4.11 (2H, s), 5.48 (1H, s), 6.97 (2H, t, J = 9Hz), 7.15 - 7.45 (7H, m).

The compounds of Example 6 to 63 were prepared in the same manner described in Example 1 to 5.

Reference 45

(±)-Ethyl 4-[(4-methylphenyl)phenylmethoxy]-1-piperidineacetate

Pale yellow liquid.
Mass spectrum m/z: 367 (M^+).
IR spectrum ν (liq) cm^{-1}: 1746 (COO-).
NMR spectrumδ ($CDCl_3$) ppm: 1.25 (3H, t, J = 7Hz), 1.66 - 2.06 (4H, m), 2.06 - 2.96 (4H, m), 2.31 (3H, s), 3.19 (2H, s), 3.28 - 3.62 (1H, m), 4.16 (2H, q, J = 7Hz), 5.47 (1H, s), 7.00 - 7.42 (9H, m).

Reference 46

(±)-Ethyl 4-[(4-methylphenyl)phenylmethoxy]-1-piperidinepropionate fume

Colorless crystals, mp 101 ~ 104 °C (EtOH-Et_2O).

Analysis for $C_{24}H_{31}NO_3 \cdot C_4H_4O_4$:			
Calculated	C, 67.59;	H, 7.09;	N, 2.81
Found	C, 67.29;	H, 7.15;	N, 2.83

Reference 47

(±)-Ethyl 4-[(4-methylphenyl)phenylmethoxy]-1-piperidinebutyrate

Yellow liquid.
Mass spectrum m/z: 395 (M^+).
IR spectrum ν (liq) cm^{-1}: 1736 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.24 (3H, t, J = 7Hz), 1.40 - 3.00 (14H,m), 2.31 (3H, s), 3.20 - 3.60 (1H, m), 4.11 (2H, q, J = 7Hz), 5.48 (1H, s), 7.00 - 7.50 (9H, m).

Reference 48

(±)-Ethyl 4[(4-methylphenyl)phenylmethoxy]-1-piperidinevalerate fumarate

Colorless needles, mp 116 ~ 117 °C (AcOEt).

Analysis for $C_{26}H_{35}NO_3 \cdot C_4H_4O_4$:			
Calculated	C, 68.55;	H, 7.48;	N, 2.66
Found	C, 68.36;	H, 7.35;	N, 2.59

Reference 49

(±)-Methyl 2-[4-[(4-methylphenyl)phenylmethoxy]piperidino]ethoxyacetate

Pale yellow liquid.
Mass spectrum m/z: 397 (M^+).
IR spectrum ν (liq) cm^{-1}: 1758 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.64 - 2.04 (4H, m), 2.04 - 2.96 (4H, m), 2.31 (3H, s), 2.60 (2H, t, J = 5.5Hz), 3.30 - 3.56 (1H, m), 3.66 (2H, t, J = 5.5Hz) 3.73 (3H, s), 4.11 (2H, s), 5.47 (1H, s), 7.00 - 7.40 (9H, m).

Reference 50

(±)-Ethyl 4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinepropionate hydrochloride

Colorless prisms, mp 142 ~ 145 °C (AcOEt).

Analysis for $C_{25}H_{33}NO_3$ • HCl:			
Calculated	C, 69.51;	H, 7.93;	N, 3.24
Found	C, 69.23;	H, 7.91;	N, 3.33

Reference 51

(±)-Methyl 4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproate

Yellow liquid.
Mass spectrum m/z: 423 (M^+).
IR spectrum ν (liq) cm^{-1}: 1738 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.09 - 2.97 (18H, m), 1.21 (3H, t, J = 7.5Hz), 2.62 (2H, q, J = 7.5Hz), 3.28 - 3.60 (1H, m), 3.65 (3H, s), 5.48 (1H, s), 7.03 - 7.50 (9H, m).

Reference 52

(±)-Ethyl 4-[(4-n-propylphenyl)phenylmethoxy]-1-piperidinepropionate hydrochloride

Colorless needles, mp 154 ~ 156 °C (AcOEt).

Analysis for $C_{26}H_{35}NO_3$ • HCl:			
Calculated	C, 70.01;	H, 8.14;	N, 3.14
Found	C, 70.00;	H, 8.13;	N, 3.21

Reference 53

(±)-Ethyl 4-[(4-n-butylphenyl)phenylmethoxy]-1-piperidinepropionate hydrochloride

Colorless needles, mp 167 ~ 170 °C (AcOEt).

Analysis for $C_{27}H_{37}NO_3$ • HCl:			
Calculated	C, 70.49;	H, 8.33;	N, 3.04
Found	C, 70.49;	H, 8.27;	N, 3.08

Reference 54

(±)-Ethyl 4-[(4-tert-butylphenyl)phenylmethoxy]-1-piperidinepropionate hydrochloride

Colorless flakes, mp 138 ~ 140.5 °C (AcOEt).

Analysis for $C_{27}H_{37}NO_3$ • HCl:			
Calculated	C, 70.49;	H, 8.33;	N, 3.04
Found	C, 70.47;	H, 8.19;	N, 3.11

Reference 55

(±)-Ethyl 4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidineacetate maleate

Colorless needles, mp 109 ~ 112 °C (Me_2CO-Et_2O).

Analysis for $C_{23}H_{29}NO_4$ • $C_4H_4O_4$:			
Calculated	C, 64.92;	H, 6.66;	N, 2.80
Found	C, 64.87;	H, 6.64;	N, 2.88

Reference 56

(±)-Ethyl 4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinepropionate fumarate

Colorless crystals, mp 109 ~ 111 °C (EtOH-Et_2O).

Analysis for $C_{24}H_{31}NO_4$ • $C_4H_4O_4$:			
Calculated	C, 65.48;	H, 6.87;	N, 2.73
Found	C, 65.37;	H, 6.82;	N, 2.64

Reference 57

(±)-Ethyl 4[(4-methoxyphenyl)phenylmethoxy]-1-piperidinebutyrate fumarate

Colorless crystals, mp 127 ~ 130 °C (EtOH-Et_2O).

Analysis for $C_{25}H_{33}NO_4$ • $C_4H_4O_4$:			
Calculated	C, 66.02;	H, 7.07;	N, 2.65
Found	C, 65.82;	H, 7.12;	N, 2.63

Reference 58

(±)-Ethyl 4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinevalerate fumarate

Pale brown prisms, mp 117 ~ 119 °C (Me_2CO-Et_2O).

Analysis for $C_{26}H_{35}NO_4 \cdot C_4H_4O_4$:			
Calculated	C, 66.53;	H, 7.26;	N, 2.59
Found	C, 66.41;	H, 7.13;	N, 2.47

Reference 59

(±)-Methyl 4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproate fumarate

Colorless flakes, mp 95 ~ 97 °C (Me_2CO-Et_2O).

Analysis for $C_{26}H_{35}NO_4 \cdot C_4H_4O_4$:			
Calculated	C, 66.53;	H, 7.26;	N, 2.59
Found	C, 66.42;	H, 7.01;	N, 2.60

Reference 60

(±)-Methyl 2-[4-[(4-methoxyphenyl)phenylmethoxy]piperidino]ethoxyacetate

Pale yellow liquid.
Mass spectrum m/z: 413 (M^+).
IR spectrum ν (liq) cm^{-1} : 1756 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.60 - 2.08 (4H, m), 2.08 - 3.00 (4H, m) , 2.61 (2H, t, J = 5.5Hz), 3.30 - 3.56 (1H, m), 3.67 (2H, t, J = 5.5Hz), 3.73 (3H, s), 3.77 (3H, s), 4.11 (2H, s), 5.47 (1H, s), 6.83 (2H, d, J = 9Hz), 7.23 (2H, d, J = 9Hz), 7.08 - 7.44 (5H, m).

Reference 61

(±)-Ethyl 4-[(4-ethoxyphenyl)phenylmethoxy]-1-piperidinepropionate fumarate

Colorless crystals, mp 149 ~ 150.5 °C (AcOEt).

Analysis for $C_{25}H_{33}NO_4 \cdot C_4H_4O_4$:			
Calculated	C, 66.02;	H, 7.07;	N, 2.65
Found	C, 65.89;	H, 7.02;	N, 2.65

Reference 62

Ethyl 4-(diphenylmethoxy)-1-piperidineacetate

Pale yellow liquid.
Mass spectrum m/z: 353 (M^+).
IR spectrum ν (liq) cm^{-1}: 1748 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.25 (3H, t, J = 7Hz), 1.56 - 2.10 (4H, m), 2.20 - 3.00 (4H, m), 3.20 (2H, s), 3.30 - 3.64 (1H, m), 4.17 (2H, q, J = 7Hz), 5.50 (1H, s), 7.08 -

7.64 (10H, m).

Reference 63

(±)-Ethyl 4-(diphenylmethoxy)-α-methyl-1-piperidineacetate

Pale yellow liquid.
Mass spectrum m/z: 367 (M^+).
IR spectrum ν (liq) cm^{-1}: 1730 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.24 (3H, t, J = 7Hz), 1.27 (3H, d, J = 7Hz), 1.50 - 2.10 (4H, m), 2.15 - 3.05 (4H, m), 3.27 (1H, q,J = 7Hz), 3.15 - 3.65 (1H, m), 4.14 (2H, q, J = 7Hz), 5.50 (1H, s), 7.05 - 7.45 (10H, m).

Reference 64

Ethyl 4-(diphenylmethoxy)-1-piperidinevalerate hydrochloride

Colorless flakes, mp 137 ~ 139 °C (AcOEt).

Analysis for $C_{25}H_{33}NO_3$ • HCl:			
Calculated	C, 69.51;	H, 7.93;	N, 3.24
Found	C, 69.50;	H, 7.86;	N, 3.33

Reference 65

Methyl 2-[4-(diphenylmethoxy)piperidino]ethoxyacetate

Colorless liquid.
Mass spectrum m/z: 383 (M^+).
IR spectrum ν (liq) cm^{-1}: 1756 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.50 - 2.97 (8H, m), 2.61 (2H, t, J = 6Hz), 3.30 - 3.60 (1H, m), 3.67(2H, t, J = 6Hz), 3.73 (3H, s), 4.11 (2H, s), 5.50 (1H, s), 7.29 (10H, s-like).

Reference 66

(±)-Ethyl 4-[(4-chlorophenyl)phenylmethoxy]-1-piperidineacetate hydrochloride

Colorless needles, mp 166 ~ 167 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{26}ClNO_3$ • HCl:			
Calculated	C, 62.27;	H, 6.41;	N, 3.30
Found	C, 62.02;	H, 6.36;	N, 3.22

Reference 67

(±)-Ethyl 4-[(4-chlorophenyl)phenylmethoxy]-1-piperidinepropionate hydrochloride

Colorless crystals, mp 187 ~ 189 °C (EtOH-Et_2O).

Analysis for $C_{23}H_{28}ClNO_3 \cdot HCl$:			
Calculated	C, 63.01;	H, 6.67;	N, 3.20
Found	C, 62.77;	H, 6.63;	N, 3.24

Reference 68

(±)-Ethyl 4-[(4-chlorophenyl)phenylmethoxy]-1-piperidinevalerate fumarate

Colorless needles, mp 125 ~ 126 °C (H_2O).

Analysis for $C_{25}H_{32}ClNO_3 \cdot C_4H_4O_4$:			
Calculated	C, 63.79;	H, 6.65;	N, 2.57
Found	C, 63.78;	H, 6.54;	N, 2.59

Reference 69

(±)-Methyl 2-[4-[(4-chlorophenyl)phenylmethoxy]piperidino]ethoxyacetate

Pale yellow liquid.

Mass spectrum m/z: 417, 419 (3:1, M^+).

IR spectrum ν (liq) cm^{-1}: 1758 (COO-).

NMR spectrumδ ($CDCl_3$) ppm: 1.60 - 1.96 (4H, m), 2.04 - 2.36 (2H, m), 2.60 (2H, t, J = 5.5Hz), 2.66 - 2.96 (2H, m), 3.26 - 3.60 (1H, m), 3.66 (2H, t, J = 5.5Hz), 3.73 (3H, s), 4.11 (2H, s), 5.47 (1H, s), 7.10 - 7.44 (9H, m).

Reference 70

(±)-Ethyl 4-[(3-chlorophenyl)phenylmethoxy]-1-piperidinepropionate hydrochloride

Colorless crystals, mp 170 ~ 172 °C (H_2O).

Analysis for $C_{23}H_{28}ClNO_3 \cdot HCl$:			
Calculated	C, 63.01;	H, 6.67;	N, 3.20
Found	C, 62.80;	H, 6.42;	N, 3.15

Reference 71

(±)-Ethyl 4-[(3-chlorophenyl)phenylmethoxy]-1-piperidinebutyrate

Pale yellow liquid.

Mass spectrum m/z: 415, 417 (3:1, M^+).

IR spectrum ν (liq) cm^{-1}: 1734 (COO-).

NMR spectrumδ ($CDCl_3$) ppm: 1.25 (3H, t, J = 7Hz), 1.50 - 3.00 (14H, m), 3.20 - 3.60 (1H, m), 4.12 (2H, q, J = 7Hz), 5.46 (1H, s), 7.10 - 7.50 (9H, m).

Reference 72

(±)-Ethyl 4-[(2-chlorophenyl)phenylmethoxy]-1-piperidinepropionate hydrochloride

Colorless crystals, mp 144 ~ 146 °C (Me_2CO-Et_2O).

Analysis for $C_{23}H_{28}ClNO_3$ • HCl:			
Calculated	C, 63.01;	H, 6.67;	N, 3.20
Found	C, 62.93;	H, 6.75;	N, 3.12

Reference 73

(±)-Ethyl 4-[(2-chlorophenyl)phenylmethoxy]-1-piperidinebutyrate

Yellowish orange liquid.
Mass spectrum m/z: 415, 417 (3:1, M^+).
IR spectrum ν (liq) cm^{-1}: 1736 (COO-).
NMR spectrumδ ($CDCl_3$) ppm: 1.24 (3H, t, J = 7Hz), 1.40 - 2.95 (14H, m), 3.20 - 3.60 (1H, m), 4.11 (2H, q, J = 7Hz), 5.97 (1H, s), 7.00 - 7.70 (9H, m).

Reference 74

(±)-Ethyl 4-[(4-fluorophenyl)phenylmethoxy]-1-piperidineacetate hydrochloride

Colorless needles, mp 167 ~ 170 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{26}FNO_3$ • HCl:			
Calculated	C, 64.78;	H, 6.67;	N, 3.43
Found	C, 64.73;	H, 6.58;	N, 3.30

Reference 75

(±)-Ethyl 4-[(4-fluorophenyl)phenylmethoxy]-1-piperidinepropionate hydrochloride

Colorless needles, mp 200 ~ 201 °C (EtOH-Et_2O).

Analysis for $C_{23}H_{28}FNO_3$ • HCl:			
Calculated	C, 65.47;	H, 6.93;	N, 3.32
Found	C, 65.17;	H, 6.87;	N, 3.34

Reference 76

(±)-Ethyl 4-[(4-fluorophenyl)phenylmethoxy]-1-piperidinebutyrate hydrochloride

Colorless needles, mp 128 ~ 131 °C (AcOEt).

Analysis for $C_{24}H_{30}FNO_3$ • HCl:			
Calculated	C, 66.12;	H, 7.17;	N, 3.21
Found	C, 66.07;	H, 7.03;	N, 3.15

Reference 77

(±)-Ethyl 4-[(4-fluorophenyl)phenylmethoxy]-1-piperidinevalerate hydrochloride

Pale brown crystals, mp 122 ~ 123 °C (AcOEt-Et_2O).

Analysis for $C_{25}H_{32}FNO_3$ • HCl:			
Calculated	C, 66.73;	H, 7.39;	N, 3.11
Found	C, 66.44;	H, 7.37;	N, 3.13

Reference 78

Ethyl 4-[bis(4-fluorophenyl)methoxy]-1-piperidineacetate hydrochloride

Colorless needless, mp 160 ~ 161.5 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{25}F_2NO_3$ • HCl:			
Calculated	C, 62.04;	H, 6.15;	N, 3.29
Found	C, 62.01;	H, 6.11;	N, 3.37

Reference 79

Ethyl 4-[bis(4-fluorophenyl)methoxy]-1-piperidinepropionatehydrochloride

Colorless crystals, mp 192~ 197 °C (Me_2CO)

Analysis for $C_{23}H_{27}F_2NO_3$ • HCl:			
Calculated	C, 62.79;	H, 6.42;	N, 3.18
Found	C, 62.75;	H, 6.36;	N, 3.18

Reference 80

Ethyl 4-[bis(4-fluorophenyl)methoxy]-1-piperidinevalerate

Yellow liquid.
Mass spectrum m/z: 431 (M^+).
IR spectrum ν (liq) cm^{-1}: 1734 (COO-).
NMR spectrumδ ($CDCl_3$) ppm: 1.25 (3H, t, J = 7Hz), 1.40 - 1.94 (8H, m), 1.98 - 2.92 (8H, m), 3.26 -

3.56 (1H, m), 4.12 (2H, q, J = 7Hz), 5.46 (1H, s), 6.99 (4H, t, J = 8.5Hz), 7.27 (4H, dd, J = 8.5, 6Hz).

Reference 81

Methyl 2-[4-[bis(4-fluorophenyl)methoxy]piperidino]ethoxyacetate

Yellowish orange liquid.
Mass spectrum m/z: 419 (M^+).
IR spectrum ν (liq) cm^{-1}: 1754 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.45 - 2.05 (4H, m), 2.05 - 3.00 (4H, m), 2.62 (2H, t, J = 5.5Hz), 3.20 - 3.60 (1H, m), 3.67 (2H, t, J = 5.5Hz), 3.74 (3H, s), 4.12 (2H, s), 5.46 (1H, s), 6.99 (4H, t, J = 8.5Hz), 7.27 (4H, dd, J = 8.5, 5.5Hz).

Reference 82

Ethyl 4-(diphenylmethylthio)-1-piperidinebutyrate

Pale yellow liquid.
Mass spectrum m/z: 397 (M^+).
IR spectrum ν (liq) cm^{-1}: 1734 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.24 (3H, t, J = 7HZ), 1.40 - 2.20 (10H, m), 2.30 (2H, t, J = 7Hz), 2.40 - 3.00 (3H, m), 4.11 (2H, q, J = 7Hz), 5.21 (1H, s), 7.00 - 7.60 (10H, m).

Reference 83

Methyl 2-[4-(diphenylmethylthio)piperidino]ethoxyacetate

Pale yellow liquid.
Mass spectrum m/z: 399 (M^+).
IR spectrum ν (liq) cm^{-1}: 1758 (COO-).
NMR spectrum δ ($CDCl_3$) ppm: 1.40 - 2.55 (7H, m), 2.58 (2H, t, J = 5.5Hz), 2.70 - 3.00 (2H, m), 3.65 (2H, t, J = 5.5Hz), 3.73 (3H, s), 4.10 (2H, s), 5.21 (1H, s), 7.15 - 7.55 (10H, m).

Reference 84

(+)-Methyl 4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproate hydrochloride

Colorless needles, mp 142.5 ~ 143.5 °C (AcOEt).
specific rotation $[\alpha]_D^{20}$ + 9.0 ° (c = 0.5, MeOH).

Analysis for $C_{26}H_{35}NO_3 \cdot HCl$:			
Calculated	C, 70.01;	H, 8.14;	N, 3.14
Found	C, 69.80;	H, 8.18;	N, 3.27

Reference 85

(-)-Methyl 4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproate hydrochloride

Colorless needles, mp 142.5 ~ 143.5 °C (AcOEt).
specific rotation $[\alpha]_D^{20}$ - 9.1 ° (c = 0.5, MeOH).

Analysis for $C_{26}H_{35}NO_3$ • HCl:			
Calculated	C, 70.01;	H, 8.14;	N, 3.14
Found	C, 69.75;	H, 8.18;	N, 3.21

Example 1

(±)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidinecaproic acid hydrochloride

A mixture of 8.29 g of (±)-methyl 4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproate hydrochloride in 40 ml of methanol and 28 ml of 2N sodium hydroxide aqueous solution was refluxed for 1 hour and concentrated. Water was added to the residue, made acidic with hydrochloric acid and extracted with chloroform. The extract was dried and concentrated. The residue was solidified by treatment with ethyl acetate and ether. The precipitate was collected by filtration to give 7.73 g of colorless crystals. The crystals were then recrystallized from a mixture of water and acetone to give 5.80g of colorless prisms, mp 168 ~ 170 °C.

Analysis for $C_{25}H_{33}NO_3$ • HCl:			
Calculated	C, 69.51;	H, 7.93;	N, 3.24
Found	C, 69.43;	H, 8.07;	N, 3.24

Example 2

4-(Diphenylmethoxy)-1-piperidinepropionic acid hydrochloride

A mixture of 3.22 g of ethyl 4-(diphenylmethoxy)-1-piperidinepropionate hydrochloride in 30 ml of methanol and 12.0 ml of 2N sodium hydroxide aqueous solution was refluxed for 1 hour and concentrated. Water was added to the residue and made acidic with hydrochloric acid. The precipitate was collected by filtration and recrystallized from water to give 2.64 g of colorless needles, mp 183 ~ 185 °C

Analysis for $C_{21}H_{25}NO_3$ • HCl • $1/2H_2O$:			
Calculated	C, 65.53;	H, 7.07;	N, 3.64
Found	C, 65.73;	H, 6.87;	N, 3.80

Example 3

4-[Bis(4-methylphenyl)methoxy]-1-piperidinepropionic acid hydrochloride

A mixture of 3.55 g of ethyl 4-[bis(4-methylphenyl)methoxy]-1-piperidinepropionate hydrochloride, 12.4 ml of 2N sodium hydroxide aqueous solution and 20 ml of methanol was refluxed for 1 hour and then concentrated. Water was added to the residue and made acidic with hydrochloric acid. The resulting precipitate was collected by filtration to give 3.29 g of colorless crystals. The crystals were recrystallized from water to give 2.63 g of colorless needles, mp 159 ~ 162 °C.

Analysis for $C_{23}H_{29}NO_3$ • HCl:			
Calculated	C, 68.39;	H, 7.49;	N, 3.47
Found	C, 68.43;	H, 7.49;	N, 3.39

Example 4

4-(Diphenylmethylthio)-1-piperidinepropionic acid hydrochloride

A mixture of 1.45 g of ethyl 4-(diphenylmethylthio)-1-piperidinepropionate in 15 ml of methanol and 5.7 ml of 2N sodium hydroxide aqueous solution was refluxed for 1 hour and concentrated. Water was added to the residue and made acidic with hydrochloric acid. The precipitate was collected by filtration and recrystallized from a mixture of ethanol and ether to give 1.04 g of colorless plates, mp 170 ~ 172 °C.

Analysis for $C_{21}H_{25}NO_2S \cdot HCl \cdot 1/2H_2O$			
Calculated	C, 62.91;	H, 6.79;	N, 3.49
Found	C, 63.03;	H, 7.03;	N, 3.31

Example 5

(±)-2-[4-(4-Fluorophenyl)phenylmethoxy]piperidino]ethoxyacetic acid

A mixture of 3.81 g of (±)-methyl 2-[4-[(4-fluorophenyl)phenylmethoxy]piperidino]ethoxyacetate in 35ml of methanol and 9.2ml of 2N sodium hydroxide aqueous solution was refluxed for 2 hours and concentrated. Water was added to the residue, made acidic with hydrochloric acid and extracted with chloroform. The extract was dried and evaporated. The resulting residue was dissolved in chloroform and the chloroform solution was made alkaline by bubbling ammonia gas through the solution. The resulting precipitate was filtered off and the filtrate was concentrated to give 2.09 g of pale brown liquid.

Mass spectrum m/z: 387 (M^+).
IR spectrum ν (liq) cm^{-1}: 1606 (COO^-)
NMR spectrum δ ($CDCl_3$) ppm: 1.73 - 2.40 (4H, m), 2.80 - 3.40 (6H, m), 3.53 - 3.93 (3H, m), 4.00 (2H, s), 5.43 (1H, s), 7.00 (2H, t, J = 8.5Hz), 7.15 - 7.50 (7H, m).

The compounds of Examples 69 to 126 were prepared in the same manner described in Examples 64 to 68.

Example 6

(±)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidineacetic acid

Colorless needles, mp 73.5 ~ 75 °C (H_2O).

Analysis for $C_{21}H_{25}NO_3 \cdot 2H_2O$:			
Calculated	C, 67.18;	H, 7.79;	N, 3.73
Found	C, 67.10;	H, 7.51;	N, 3.81

Example 7

(±)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 157 ~ 159 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{27}NO_3 \cdot HCl$:			
Calculated	C, 67.77;	H, 7.24;	N, 3.59
Found	C, 67.63;	H, 6.99;	N, 3.54

Example 8

(±)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidinebutyric acid hydrochloride

Colorless crystals, mp 151 ~ 153 °C (EtOH-Et_2O).

Analysis for $C_{23}H_{29}NO_3$ • HCl:			
Calculated	C, 68.39;	H, 7.49;	N, 3.47
Found	C, 68.19;	H, 7.33;	N, 3.27

Example 9

(±)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidinevaleric acid hydrochloride

Colorless prisms, mp 171.5 ~ 173 °C (MeOH-Et_2O).

Analysis for $C_{24}H_{31}NO_3$ • HCl:			
Calculated	C, 68.97;	H, 7.72;	N, 3.35
Found	C, 68.81;	H, 7.49;	N, 3.29

Example 10

(±)-2-[4-[(4-Methylphenyl)phenylmethoxy]piperidino]ethoxyacetic acid

Pale yellow liquid.
Mass spectrum m/z: 384 (M^+ +1).
IR spectrum ν (liq) cm^{-1}: 1592 (COO^-)
NMR spectrumδ ($CDCl_3$) ppm: 1.88 - 2.46 (4H, m), 2.32 (3H, s), 2.88 - 3.38 (6H, m), 3.64 - 3.95 (3H, m), 4.01 (2H, s), 5.41 (1H, s), 7.00 - 7.40 (9H, m).

Example 11

(±)-4-[(4-Ethylphenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 139.5 ~ 142.5 °C (Me_2CO-Et_2O)

Analysis for $C_{23}H_{29}NO_3$ • HCl:			
Calculated	C, 68.39;	H, 7.49;	N, 3.47
Found	C, 68.29;	H, 7.65;	N, 3.52

Example 12

(±)-4-[(4-Ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid hydrochloride

Colorless crystals, mp 132 ~ 137 °C (Me_2CO).

Analysis for $C_{26}H_{35}NO_3$ • HCl:			
Calculated	C, 70.01;	H, 8.14;	N, 3.14
Found	C, 69.81;	H, 8.15;	N, 3.04

Example 13

(±)-4-[(4-n-Propylphenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 140 ~ 143 °C (Me_2CO-Et_2O)

Analysis for $C_{24}H_{31}NO_3$ • HCl:			
Calculated	C, 68.97;	H, 7.72;	N, 3.35
Found	C, 68.85;	H, 7.75;	N, 3.29

Example 14

(±)-4-[(4-n-Butylphenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 127 ~ 130 °C (Me_2CO-iso-Pr_2O).

Analysis for $C_{25}H_{33}NO_3$ • HCl • 1/4H_2O:			
Calculated	C, 68.79;	H, 7.97;	N, 3.21
Found	C, 68.69;	H, 7.98;	N, 3.24

Example 15

(±)-4-[4-tert-Butylphenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Pale yellow crystals, mp 103 ~ 105 °C (Me_2CO-Et_2O).

Analysis for $C_{25}H_{33}NO_3$ • HCl:			
Calculated	C, 69.51;	H, 7.93;	N, 3.24
Found	C, 69.50;	H, 8.03;	N, 3.22

Example 16

(±)-4-[(4-Methoxyphenyl)phenylmethoxy]-1-piperidineacetic acid

Pale yellow crystals, mp 84 ~ 85 °C (H_2O).

Analysis for $C_{21}H_{25}NO_4 \cdot 2H_2O$:			
Calculated	C, 64.43;	H, 7.47;	N, 3.58
Found	C, 64.70;	H, 7.16;	N, 3.41

Example 17

(±)-4-[(4-Methoxyphenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 146 ~ 148 °C (EtOH-AcOEt).

Analysis for $C_{22}H_{27}NO_4 \cdot HCl$:			
Calculated	C, 65.10;	H, 6.95;	N, 3.45
Found	C, 64.99;	H, 6.83;	N, 3.45

Example 18

(±)-4-[(4-Methoxyphenyl)phenylmethoxy]-1-piperidinebutyric acid hydrochloride

Colorless crystals, mp 135 ~ 137 °C (EtOH-AcOEt).

Analysis for $C_{23}H_{29}NO_4 \cdot HCl \cdot 1/4H_2O$:			
Calculated	C, 65.08;	H, 7.24;	N, 3.30
Found	C, 64.96;	H, 7.01;	N, 3.28

Example 19

(±)-4-[(4-Methoxyphenyl)phenylmethoxy]-1-piperidinevaleric acid hydrochloride

Colorless prisms, mp 150 ~ 151 °C (MeOH-Et_2O).

Analysis for $C_{24}H_{31}NO_4 \cdot HCl$:			
Calculated	C, 66.42;	H, 7.43;	N, 3.23
Found	C, 66.18;	H, 7.43;	N, 3.26

Example 20

(±)-4-[(4-Methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid hydrochloride

Colorless plates, mp 148 ~ 150 °C (MeOH-Et_2O).

Analysis for $C_{25}H_{33}NO_4$ • HCl:			
Calculated	C, 67.03;	H, 7.65;	N, 3.13
Found	C, 66.84;	H, 7.78;	N, 3.16

Example 21

(±)-2-[4-[(4-Methoxyphenyl)phenylmethoxy]piperidino)ethoxyacetic acid

Pale yellow liquid.
Mass spectrum m/z: 400 (M^+ + 1)
IR spectrum ν (liq) cm^{-1}: 1592 ($(COO^-$)
NMR spectrum δ ($CDCl_3$) ppm: 1.80 - 2.44 (4H, m), 2.88 - 3.36 (6H, m), 3.64 - 3.96 (3H, m), 3.78 (3H, s), 4.03 (2H, s), 5.40 (1H, s), 6.84 (2H, d, J = 9Hz), 7.22 (2H, d, J = 9Hz), 7.12 - 7.40 (5H, m).

Example 22

(±)-4-[(4-Ethoxyphenyl)phenylmethoxy]-1-piperidinepropionic acid

Colorless crystals, mp 75 ~ 78 °C (AcOEt-Et_2O).

Analysis for $C_{23}H_{29}NO_4$ • H_2O:			
Calculated	C, 68.80;	H, 7.78;	N, 3.49
Found	C, 69.05;	H, 7.83;	N, 3.52

Example 23

4-(Diphenylmethoxy)-1-piperidineacetic acid hydrochloride

Colorless crystals, mp 193 ~ 194 °C (MeOH-Et_2O).

Analysis for $C_{20}H_{23}NO_3$ • HCl:			
Calculated	C, 66.38;	H, 6.68;	N, 3.87
Found	C, 66.33;	H, 6.71;	N, 3.84

Example 24

(±)-4-(Diphenylmethoxy)-α -methyl-1-piperidineacetic acid hydrochloride

Colorless amorphous solid, mp 63~ 65 °C (Me_2CO-Et_2O)
Mass spectrum m/z: 339 (M^+)
IR spectrum ν (KBr) cm^{-1}: 1736 (COOH).
NMR spectrum δ (DMSO-d_6) ppm: 1.41 (3H, d, J = 7Hz), 1.62 - 2.30 (4H, m), 2.82 - 3.96 (5H, m), 3.79 (1H, q, J = 7Hz), 5.63 (1H, s), 7.07 - 7.55 (10H, m).

Example 25

4-(Diphenylmethoxy)-1-piperidinevaleric acid hydrochloride Colorless crystals, mp 150 ~ 151 °C (H_2O).

Analysis for $C_{23}H_{29}NO_3 \cdot HCl \cdot H_2O$			
Calculated	C, 65.47;	H, 7.64;	N, 3.32
Found	C, 65.50;	H, 7.67;	N, 3.27

Example 26

2-[4-(Diphenylmethoxy)piperidino]ethoxyacetic acid hydrochloride

Colorless needles, mp 161 ~ 162 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{27}NO_4 \cdot HCl$:			
Calculated	C, 65.10;	H, 6.95;	N, 3.45
Found	C, 65.00;	H, 6.87;	N, 3.38

Example 27

(±)-4-[(4-Chlorophenyl)phenylmethoxy]-1-piperidineacetic acid hydrochloride

Pale yellow amorphous solid, mp 125 ~ 130 °C (Me_2CO-Et_2O).

Analysis for $C_{20}H_{22}ClNO_3 \cdot HCl$:			
Calculated	C, 60.61;	H, 5.85;	N, 3.53
Found	C, 60.62;	H, 6.09;	N, 3.36

Example 28

(±)-4-[(4-Chlorophenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 179 ~ 181 °C (MeOH-Et_2O).

Analysis for $C_{21}H_{24}ClNO_3 \cdot HCl$:			
Calculated	C, 61.47;	H, 6.14;	N, 3.41
Found	C, 61.46;	H, 6.17;	N, 3.50

Example 29

(±)-4-[(4-Chlorophenyl)phenylmethoxy]-1-piperidinevaleric acid hydrochloride

Colorless prisms, mp 142.5 ~ 144 °C (EtOH-Et_2O).

Analysis for $C_{23}H_{28}ClNO_3$ • HCl:			
Calculated	C, 63.01;	H, 6.67;	N, 3.20
Found	C, 63.05;	H, 6.57;	N, 3.03

Example 30

(±)-2-[4-[(4-Chlorophenyl)phenylmethoxy]piperidino]ethoxyacetic acid

Pale yellow liquid.
Mass spectrum m/z: 403, 405 (3:1, M^+).
IR spectrum ν (liq) cm^{-1}: 1596 (COO^-).
NMR spectrum δ ($CDCl_3$) ppm: 1.73 - 2.35 (4H, m), 2.77 - 3.30 (6H, m), 3.55 - 3.89 (3H, m), 3.95 (2H, s), 5.42 (1H, s), 7.07 - 7.47 (9H, m).

Example 31

(±)-4$^-$[(3-Chlorophenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 116 ~ 120 °C (H_2O).

Analysis for $C_{21}H_{24}ClNO_3$ • HCl:			
Calculated	C, 61.47;	H, 6.14;	N, 3.41
Found	C, 61.70;	H, 6.25;	N, 3.42

Example 32

(±)-4-[(3-Chlorophenyl)phenylmethoxy]-1-piperidinebutyric acid hydrochloride

Colorless crystals, mp 134 ~ 135 °C (Me_2CO-Et_2O).

Analysis for $C_{22}H_{26}ClNO_3$ • HCl:			
Calculated	C, 62.27;	H, 6.41;	N, 3.30
Found	C, 62.16;	H, 6.36;	N, 3.39

Example 33

(±)-4-[(2-Chlorophenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 164 ~ 166 °C (H_2O).

Analysis for $C_{21}H_{24}ClNO_3$ • HCl:			
Calculated	C, 61.47;	H, 6.14;	N, 3.41
Found	C, 61.39;	H, 6.16;	N, 3.42

Example 34

(±)-4-[(2-Chlorophenyl)phenylmethoxy]-1-piperidinebutyric acid hydrochloride

Colorless crystals, mp 154.5 ~ 156 °C (H_2O).

Analysis for $C_{22}H_{26}ClNO_3$ • HCl:			
Calculated	C, 62.27;	H, 6.41;	N, 3.30
Found	C, 62.49;	H, 6.35;	N, 3.34

Example 35

(±)-4-[(4-Fluorophenyl)phenylmethoxy]-1-piperidineacetic acid

Colorless needles, mp 147 ~ 148 °C (EtOH-Et_2O).

Analysis for $C_{20}H_{22}FNO_3$ • H_2O:			
Calculated	C, 66.47	H, 6.69;	N, 3.88
Found	C, 66.52;	H, 6.58;	N, 3.83

Example 36

(±)-4-[(4-Fluorophenyl)phenylmethoxy]-1-piperidinepropionic acid hydrochloride

Colorless needles, mp 170 ~ 171 °C (MeOH-Me_2CO).

Analysis for $C_{21}H_{24}FNO_3$ • HCl:			
Calculated	C, 64.04;	H, 6.40;	N, 3.56
Found	C, 63.80;	H, 6.39;	N, 3.59

Example 37

(±)-4-[(4-Fluorophenyl)phenylmethoxy]-1-piperidinebutyric acid hydrochloride

Colorless needles, mp 199 ~ 200 °C (MeOH-Me_2CO).

Analysis for $C_{22}H_{26}FNO_3$ • HCl:			
Calculated	C, 64.78;	H, 6.67;	N, 3.43
Found	C, 64.69;	H, 6.67;	N, 3.45

Example 38

(±)-4-[(4-Fluorophenyl)phenylmethoxy]-1-piperidinevaleric acid hydrochloride

Colorless crystals, mp 181 ~ 184 °C (EtOH-Et_2O).

Analysis for $C_{23}H_{28}FNO_3$ • HCl:			
Calculated	C, 65.47;	H, 6.93;	N, 3.32
Found	C, 65.27;	H, 6.61;	N, 3.22

Example 39

4-[Bis(4-fluorophenyl)methoxy]-1-piperidineacetic acid

Colorless needles, mp 126.5 ~ 127.5 °C (H_2O)

Analysis for $C_{20}H_{21}F_2NO_3$ • 1/2H_2O:			
Calculated	C, 64.85;	H, 5.99;	N, 3.78
Found	C, 64.65;	H, 6.27;	N, 3.83

Example 40

4-[Bis(4-fluorophenyl)methoxy]-1-piperidinepropionic acid hydrochloride

Colorless crystals, mp 166 ~ 168 °C (H_2O)

Analysis for $C_{21}H_{23}F_2NO_3$ • HCl:			
Calculated	C, 61.24;	H, 5.87;	N, 3.40
Found	C, 61.12;	H, 5.89;	N, 3.44

Example 41

4-[Bis(4-fluorophenyl)methoxy]-1-piperidinevaleric acid hydrochloride

Pale brown needles, mp 117 ~ 118 °C (EtOH-Et_2O).

Analysis for $C_{23}H_{27}F_2NO_3 \cdot HCl \cdot H_2O$:			
Calculated	C, 60.32;	H, 6.60;	N, 3.06
Found	C, 60.43;	H, 6.83;	N, 3.13

Example 42

2-[4-[Bis(4-fluorophenyl)methoxy]piperidino]ethoxyacetic acid

Pale brown liquid.
Mass spectrum m/z: 405 (M^+)
IR spectrum ν (liq) cm^{-1}: 1604 (COO^-).
NMR spectrum δ ($CDCl_3$) ppm: 1.60 - 2.47 (4H, m), 2.73 - 3.40 (6H, m), 3.53 - 3.93 (3H, m), 3.98 (2H, s), 5.42 (1H, s), 7.00 (4H, t, J = 9Hz), 7.27 (4H, dd, J = 9, 5.5Hz).

Example 43

4-(Diphenylmethylthio)-1-piperidinebutyric acid hydrochloride

Colorless needles, mp 196 ~ 199 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{27}NO_2S \cdot HCl \cdot 1/2H_2O$:			
Calculated	C, 63.67;	H, 7.04;	N, 3.38
Found	C, 63.80;	H, 6.82;	N, 3.35

Example 44

2-[4-(Diphenylmethylthio)piperidino]ethoxyacetic acid hydrochloride

Colorless pillars, mp 140 ~ 142 °C (EtOH-Et_2O).

Analysis for $C_{22}H_{27}NO_3S \cdot HCl$:			
Calculated	C, 62.62;	H, 6.69;	N, 3.32
Found	C, 62.54;	H, 6.63;	N, 3.31

Example 45

(+)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidinecaproic acid hydrochloride

Colorless crystals, mp 164.5 ~ 167 °C (H_2O-Me_2CO).
specific rotation $[\alpha]_D^{20}$ + 9.5° (c = 0.5, MeOH).

Analysis for $C_{25}H_{33}NO_3$ • HCl:			
Calculated	C, 69.51;	H, 7.93;	N, 3.24
Found	C, 69.70;	H, 8.07;	N, 3.36

Example 46

(-)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidinecaproic acid hydrochloride

Colorless crystals, mp 165.5 ~ 168 °C (H_2O-Me_2CO).
specific rotation $[\alpha]_D^{20}$ - 9.5 ° (c = 0.5, MeOH).

Analysis for $C_{23}H_{33}NO_3$ • HCl:			
Calculated	C, 69.51;	H, 7.93;	N, 3.24
Found	C, 69.50;	H, 8.01;	N, 3.28

Example 47

Tablets of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	10 mg
Lactose	q.s.
Corn starch	34 mg
Magnesium stearate	2 mg
Hydroxypropylmethylcellulose	8 mg
Polyethyleneglycol 6000	0.5 mg
Titanium oxide	0.5 mg
	120 mg

Example 48

Capsules of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	10 mg
Lactose	q.s.
Calcium carboxymethylcellulose	15 mg
Hydroxypropylcellulose	2 mg
Magnesium stearate	2 mg
	100 mg

Example 49

Powder of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	20 mg
Lactose	q.s.
D-Mannitol	500 mg
Hydroxypropylcellulose	5 mg
Talc	2 mg
	1000 mg

Example 50

Injections of a pharmaceutical preparation according to the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	1 mg
Glucose	50 mg
Hydrochloric acid	q.s.
Distilled water for injection	q.s.
	2 ml

Example 51

Suppositories of a pharmaceutical preparation of the present invention are prepared in the usual manner using the following constituents:

Compound of the present invention	5 mg
Hard fat	1295 mg
	1300 mg

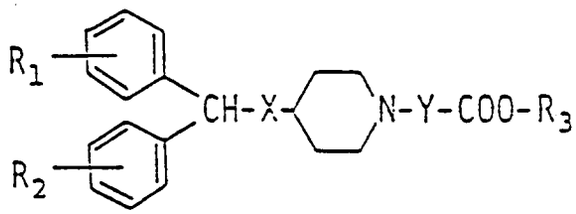
Example 52

Plasters of a pharmaceutical preparation according to the present invention

Compound of the present invention	10 mg
Gelatin	1100 mg
Polyvinylalcohol	250 mg
Methylcellulose	100 mg
Glycerin	1500 mg
Kaolin	850 mg
Sodium polyacrylate	50 mg
Polybutene	150 mg
Purified water	990 mg
	5000 mg

Claims

1. A piperidine derivative represented by the following general formula (I):



(I)

wherein R_1 and R_2 are the same or different and each independently represents a hydrogen atom, a halogen atom, a C_1 - C_4 alkyl group, or a C_1 - C_4 alkoxy group; R_3 represents a hydrogen atom; X represents an oxygen atom or a sulfur atom; Y represents an alkylene group having 1 to 4 carbon atoms which may be optionally substituted with a C_1 - C_4 alkyl group, or Y represents an -A-O-B-group wherein A and B are the same or different and each independently represents an alkylene group having 1 to 3 carbon atoms which may be optionally substituted with a C_1 - C_4 alkyl group; and pharmacologically acceptable salts of the compounds of formula (I).

2. (±)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid and pharmacologically acceptable salts thereof.

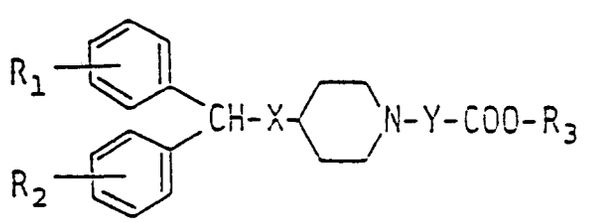
3. (±)-4-[(4-methoxyphenyl)phenylmethoxy]-1-piperidinecaproic acid and pharmacologically acceptable salts thereof.

4. (±)-4-[(4-ethylphenyl)phenylmethoxy]-1-piperidinecaproic acid and pharmacologically acceptable salts thereof.

5. (+)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid and pharmacologically acceptable salts thereof.

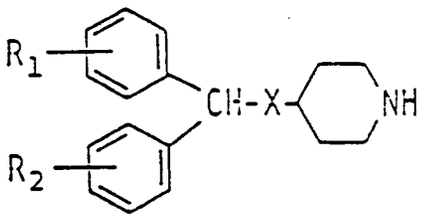
6. (-)-4-[(4-methylphenyl)phenylmethoxy]-1-piperidinecaproic acid and pharmacologically acceptable salts thereof.

7. A process for preparing a piperidine derivative of claim 1 represented by the following general formula (I):



(I)

wherein R_1 and R_2 are the same or different and each independently represents a hydrogen atom, a halogen atom, a C_1 - C_4 alkyl group, or a C_1 - C_4 alkoxy group; R_3 represents a hydrogen atom; X represents an oxygen atom or a sulfur atom; and Y represents an alkylene group having 1 to 4 carbon atoms which may be optionally substituted with a C_1 - C_4 alkyl group, or Y represents an -A-O-B-group wherein A and B are the same or different and each independently represents an alkylene group having 1 to 3 carbon atoms which may be optionally substituted with a C_1 - C_4 alkyl group; wherein said process comprises the steps of reacting a piperidine derivative represented by the following general formula (II):



(II)

wherein R_1, R_2 and X are the same as those defined above, with a compound represented by Z-Y-COO-R_3 (IIIa) or CH_2 = CHCOO-R_3 (IIIb) wherein R_3 and Y are the same as those defined above, and Z represents a halogen atom, and followed by the step of hydrolysis in a solvent by using an acid or a base, if necessary.

8. A process according to claim 7, wherein said step of reacting is carried out in the presence of a solvent.

9. A process according to claim 7, wherein said step of reacting is carried out in the absence of a solvent.

10. A process according to claim 7, wherein said step of reacting is carried out in the presence of a base.

11. A process according to claim 7, wherein said step of reacting is carried out in the absence of a base.

12. An antihistaminic and antiallergic agent comprising an effective amount of a piperidine derivative of claims 1 to 6.

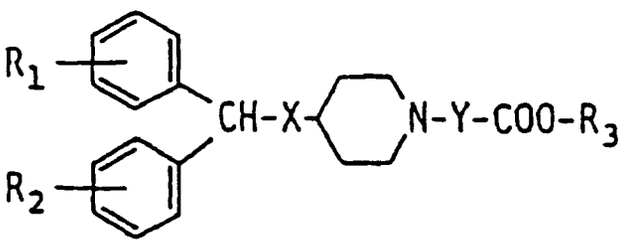
13. A pharmaceutical composition for the treatment of an allergic disease comprising an effective amount of a piperidine derivative of claims 1 to 6.

14. Use of (a) the piperidine derivative of claims 1 to 6; (b) a pharmacologically acceptable salt of the compound of claims 1 to 6; (c) an antihistaminic and antiallergic agent comprising the compounds of claims 1 to 6; or (d) a pharmaceutical composition comprising the compounds of claims 1 to 6 for the preparation of a pharmaceutical composition for the treatment of allergic disease.

15. Use according to a claim 14, wherein said treatment is performed on a human being.

Patentansprüche

1. Piperidin-Derivat, dargestellt durch folgende allgemeine Formel (I):



(I)

worin R_1 und R_2 gleich oder verschieden sind und jeweils unabhängig ein Wasserstoff-Atom, ein Halogen-Atom, eine C_1-C_4-Alkyl-Gruppe oder eine C_1-C_4-Alkoxy-Gruppe bedeuten; R_3 ein Wasserstoff-Atom bedeutet; X ein Sauerstoff-Atom oder ein Schwefel-Atom bedeutet; Y eine Alkylen-Gruppe mit 1 bis 4 Kohlenstoff-Atomen bedeutet, die gegebenenfalls mit einer C_1-C_4-Alkyl-Gruppe substituiert sein können, oder Y eine -A-O-B-Gruppe bedeutet, worin A und B gleich oder verschieden sind und jeweils unabhängig eine Alkylen-Gruppe mit 1 bis 3 Kohlenstoff-Atomen bedeuten, die gegebenenfalls mit einer C_1-C_4-Alkyl-Gruppe substituiert sein können; sowie pharmakologisch annehmbare Salze der Verbindung der Formel (I).

2. (±)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidincapronsäure und pharmakologisch annehmbare Salze derselben.

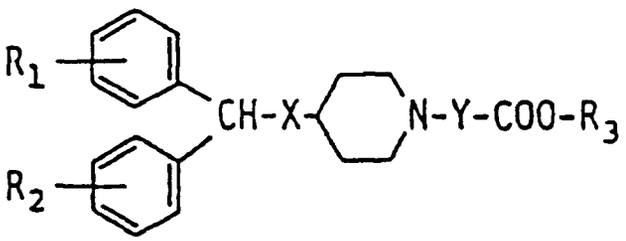
3. (±)-4-[(4-Methoxyphenyl)phenylmethoxy]-1-piperidincapronsäure und pharmakologisch annehmbare Salze derselben.

4. (±)-4-[(4-Ethylphenyl)phenylmethoxy]-1-piperidincapronsäure und pharmakologisch annehmbare Salze derselben.

5. (+)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidincapronsäure und pharmakologisch annehmbare Salze derselben.

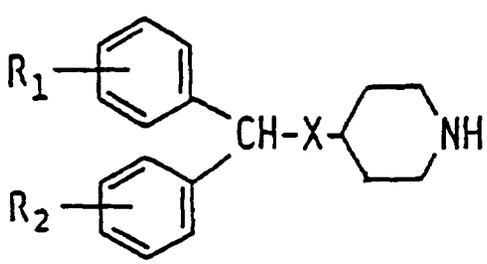
6. (-)-4-[(4-Methylphenyl)phenylmethoxy]-1-piperidincapronsäure und pharmakologisch annehmbare Salze derselben.

7. Verfahren zur Herstellung eines Piperidin-Derivats nach Anspruch 1, dargestellt durch folgende allgemeine Formel (I):



(I)

worin R_1 und R_2 gleich oder verschieden sind und jeweils unabhängig ein Wasserstoff-Atom, ein Halogen-Atom, eine C_1-C_4-Alkyl-Gruppe oder eine C_1-C_4-Alkoxy-Gruppe bedeuten; R_3 ein Wasserstoff-Atom bedeutet; X ein Sauerstoff-Atom oder ein Schwefel-Atom bedeutet; Y eine Alkylen-Gruppe mit 1 bis 4 Kohlenstoff-Atomen bedeutet, die gegebenenfalls mit einer C_1-C_4-Alkyl-Gruppe substituiert sein können, oder Y eine -A-O-B-Gruppe bedeutet, worin A und B gleich oder verschieden sind und jeweils unabhängig eine Alkylen-Gruppe mit 1 bis 3 Kohlenstoff-Atomen bedeuten, die gegebenenfalls mit einer C_1-C_4-Alkyl-Gruppe substituiert sein können;
umfassend die Schritte der Umsetzung eines Piperidin-Derivats nach Anspruch 1, dargestellt durch folgende allgemeine Formel (II):



(II)

worin R_1 und R_2 die gleichen wie die vorstehend definierten sind, mit einer Verbindung, dargestellt durch Z-Y-COO-R_3 (IIIa) oder CH_2 = CHCOO-R_3 (IIIb), worin R_3 und Y die gleichen wie die vorstehend definierten sind, und Z ein Halogen-Atom bedeutet, worauf sich der Schritt einer Hydrolyse in einem Lösungsmittel anschließt, falls nötig durch Verwendung einer Säure oder Base.

8. Verfahren nach Anspruch 7, wobei der Schritt der Umsetzung in Gegenwart eines Lösungsmittels durchgeführt wird.

9. Verfahren nach Anspruch 7, wobei der Schritt der Umsetzung in Abwesenheit eines Lösungsmittels durchgeführt wird.

10. Verfahren nach Anspruch 7, wobei der Schritt der Umsetzung in Gegenwart einer Base durchgeführt wird.

11. Verfahren nach Anspruch 7, wobei der Schritt der Umsetzung in Abwesenheit einer Base durchgeführt wird.

12. Antihistaminikum und Antiallergikum, umfassend eine wirksame Menge eines Piperidin-Derivats nach den Ansprüchen 1 bis 6.

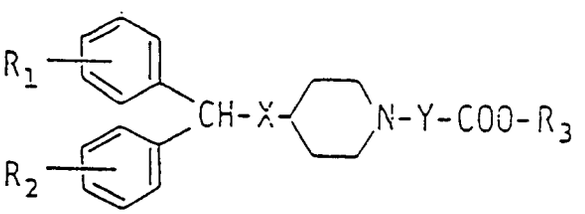
13. Pharmazeutische Zusammensetzung zur Behandlung eines allergischen Leidens, umfassend eine wirksame Menge eines Piperidin-Derivats nach den Ansprüchen 1 bis 6.

14. Verwendung von (a) des Piperidin-Derivats nach den Ansprüchen 1 bis 6, (b) eines pharmakologisch annehmbaren Salzes der Verbindung nach den Ansprüchen 1 bis 6, (c) eines Antihistaminikums und Antiallergikums, umfassend die Verbindungen nach den Ansprüchen 1 bis 6 zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung allergischer Leiden.

15. Verwendung nach Anspruch 14, wobei die Behandlung am Menschen durchgeführt wird.

Revendications

1. Un dérivé de pipéridine représenté par la formule générale suivante (I) :



(I)

dans laquelle R_1 et R_2 sont identiques ou différents et chacun représente indépendamment un atome d'hydrogène, un atome d'halogène, un groupe alkyle en C_1-C_4 ou un groupe alcoxy en C_1-C_4 ; R_3 représente un atome d'hydrogène ; X représente un atome d'oxygène ou un atome de soufre ; Y représente un groupe alkylène ayant 1 à 4 atomes de carbone qui peuvent être substitués optionnellement par un groupe alkyle en C_1-C_4, ou bien Y représente un groupe-A-O-B dans lequel A et B sont identiques ou différents et chacun représente indépendamment un groupe alkylène ayant 1 à 3 atomes de carbone qui peuvent être substitués optionnellement par un groupe alkyle en C_1-C_4 ; et des sels acceptables pharmacologiquement des composés de formule (I).

2. L'acide (±)-4-[(4-méthylphényl)phénylméthoxy]-1-pipéridine-caproïque et ses sels acceptables pharmacologiquement.

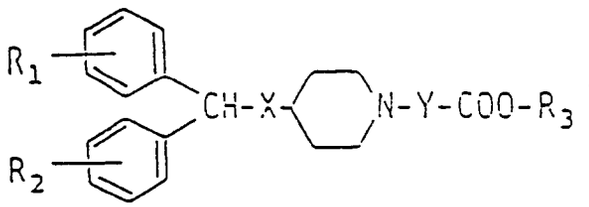
3. L'acide (±)-4-[(4-méthoxyphényl)phénylméthoxy]-1-pipéridine-caproïque et ses sels acceptables pharmacologiquement.

4. L'acide (±)-4-[(4-éthylphényl)phénylméthoxy]-1-pipéridine-caproïque et ses sels acceptables pharmacologiquement.

5. L'acide (+)-4-[(4-méthylphényl)phénylméthoxy]-1-pipéridine-caproïque et ses sels acceptables pharmacologiquement.

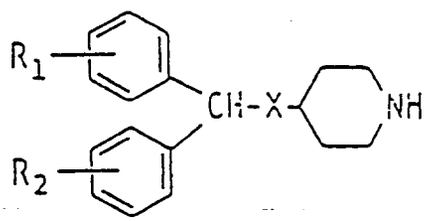
6. L'acide (-)-4-[(4-méthylphényl)phénylméthoxy]-1-pipéridine-caproïque et ses sels acceptables pharmacologiquement.

7. Un procédé pour préparer un dérivé de pipéridine de la revendication 1 représenté par la formule générale suivante (I):



(I)

dans laquelle R_1 et R_2 sont identiques ou différents et chacun représente indépendamment un atome d'hydrogène, un atome d'halogène, un groupe alkyle en C_1-C_4 ou un groupe alcoxy en C_1-C_4 ; R_3 représente un atome d'hydrogène ; X représente un atome d'oxygène ou un atome de soufre ; et Y représente un groupe alkylène ayant 1 à 4 atomes de carbone qui peuvent être substitués optionnellement par un groupe alkyle en C_1-C_4, ou bien Y représente un groupe-A-O-B dans lequel A et B sont identiques ou différents et chacun représente indépendamment un groupe alkylène ayant 1 à 3 atomes de carbone qui peuvent être substitués optionnellement par un groupe alkyle en C_1-C_4 ; dans lequel ledit procédé comprend les étapes de réaction d'un dérivé de pipéridine représenté par la formule générale suivante (II) :



(II)

dans laquelle R_1, R_2 et X sont identiques à ceux définis ci-dessus, avec un composé représenté par Z-Y-COO-R_3 (IIIa) ou CH_2 = CHCOO-R_3 (IIIb) dans lesquelles R_3 et Y sont identiques à ceux définis ci-dessus et Z représente un atome d'halogène et suivie par l'étape d'hydrolyse dans un solvant en utilisant un acide ou une base, si nécessaire.

8. Un procédé selon la revendication 7,
dans lequel ladite étape de réaction est réalisée en présence d'un solvant.

9. Un procédé selon la revendication 7,
dans lequel ladite étape de réaction est réalisée en l'absence d'un solvant.

10. Un procédé selon la revendication 7,
dans lequel ladite étape de réaction est réalisée en présence d'une base.

11. Un procédé selon la revendication 7,
dans lequel ladite étape de réaction est réalisée en l'absence d'une base.

12. Un agent antihistaminique et antiallergique comprenant une quantité efficace d'un dérivé de pipéridine des revendications 1 à 6.

13. Une composition pharmaceutique pour le traitement d'une maladie allergique comprenant une quantité efficace d'un dérivé de pipéridine des revendications 1 à 6.

14. Utilisation de (a) le dérivé de pipéridine des revendications 1 à 6 ; (b) un sel acceptable pharmacologiquement du composé des revendications 1 à 6 ; (c) un agent antihistaminique et antiallergique comprenant les composés des revendications 1 à 6; ou (d) une composition pharmaceutique comprenant les composés des revendications 1 à 6 pour la préparation d'une composition pharmaceutique pour le traitement d'une maladie allergique.

15. Utilisation conforme à une revendication 14,
dans laquelle ledit traitement est effectué sur un être humain.